

SULFIDE AND DISULFIDE COMPOUNDS AND COMPOSITIONS FOR CHOLESTEROL MANAGEMENT AND RELATED USES

This application is a continuation-in-part application of pending U.S. Application No. 09/976,898, filed October 11, 2001, which is incorporated herein by reference in its entirety.

1. Field of The Invention

The present invention relates to sulfide and disulfide compounds and pharmaceutically acceptable salts, hydrates, solvates, or mixtures thereof; compositions comprising a sulfoxide or bis-sulfoxide compound or a pharmaceutically acceptable salt, hydrate, solvate, or a mixture thereof; and methods for treating or preventing a disease or disorder such as, but not limited to, aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (*e.g.*, Syndrome X), and a thrombotic disorder, which method comprise administering a sulfide or bis-sulfide compound or composition of the invention. The compounds of the invention can also treat or prevent inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (*e.g.*, Crohn's Disease, ulcerative colitis), arthritis (*e.g.*, rheumatoid arthritis, osteoarthritis), autoimmune disease (*e.g.*, systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism.

2. Background of The Invention

Obesity, hyperlipidemia, and diabetes have been shown to play a causal role in atherosclerotic cardiovascular diseases, which currently account for a considerable proportion of morbidity in Western society. Further, one human disease, termed "Syndrome X" or "Metabolic Syndrome", is manifested by defective glucose metabolism (insulin resistance), elevated blood pressure (hypertension), and a blood lipid imbalance (dyslipidemia). *See e.g.* Reaven, 1993, *Annu. Rev. Med.* 44:121-131.

The evidence linking elevated serum cholesterol to coronary heart disease is overwhelming. Circulating cholesterol is carried by plasma lipoproteins, which are particles of complex lipid and protein composition that transport lipids in the blood. Low density lipoprotein (LDL) and high density lipoprotein (HDL) are the major cholesterol-carrier proteins. LDL is believed to be responsible for the delivery of cholesterol from the liver, where it is synthesized or obtained from dietary sources, to extrahepatic tissues in the body. The term “reverse cholesterol transport” describes the transport of cholesterol from extrahepatic tissues to the liver, where it is catabolized and eliminated. It is believed that plasma HDL particles play a major role in the reverse transport process, acting as scavengers of tissue cholesterol. HDL is also responsible for the removal of non-cholesterol lipid, oxidized cholesterol and other oxidized products from the bloodstream.

Atherosclerosis, for example, is a slowly progressive disease characterized by the accumulation of cholesterol within the arterial wall. Compelling evidence supports the belief that lipids deposited in atherosclerotic lesions are derived primarily from plasma apolipoprotein B (apo B)-containing lipoproteins, which include chylomicrons, CLDL, IDL and LDL. The apo B-containing lipoprotein, and in particular LDL, has popularly become known as the “bad” cholesterol. In contrast, HDL serum levels correlate inversely with coronary heart disease. Indeed, high serum levels of HDL are regarded as a negative risk factor. It is hypothesized that high levels of plasma HDL are not only protective against coronary artery disease, but may actually induce regression of atherosclerotic plaque (*e.g.*, see Badimon *et al.*, 1992, *Circulation* 86:(Suppl. III)86-94; Dansky and Fisher, 1999, *Circulation* 100:1762-3.). Thus, HDL has popularly become known as the “good” cholesterol.

2.1 Cholesterol Transport

The fat-transport system can be divided into two pathways: an exogenous one for cholesterol and triglycerides absorbed from the intestine and an endogenous one for cholesterol and triglycerides entering the bloodstream from the liver and other non-hepatic tissue.

In the exogenous pathway, dietary fats are packaged into lipoprotein particles called chylomicrons, which enter the bloodstream and deliver their triglycerides to adipose tissue for storage and to muscle for oxidation to supply energy. The remnant of the chylomicron, which contains cholesteryl esters, is removed from the circulation by a specific receptor found only on liver cells. This cholesterol then becomes available again for cellular metabolism or for recycling to extrahepatic tissues as plasma lipoproteins.

In the endogenous pathway, the liver secretes a large, very-low-density lipoprotein particle (VLDL) into the bloodstream. The core of VLDL consists mostly of triglycerides synthesized in the liver, with a smaller amount of cholesteryl esters either synthesized in the liver or recycled from chylomicrons. Two predominant proteins are displayed on the surface of VLDL, apolipoprotein B-100 (apo B-100) and apolipoprotein E (apo E), although other apolipoproteins are present, such as apolipoprotein CIII (apo CIII) and apolipoprotein CII (apo CII). When a VLDL reaches the capillaries of adipose tissue or of muscle, its triglyceride is extracted. This results in the formation of a new kind of particle called intermediate-density lipoprotein (IDL) or VLDL remnant, decreased in size and enriched in cholesteryl esters relative to a VLDL, but retaining its two apoproteins.

In human beings, about half of the IDL particles are removed from the circulation quickly, generally within two to six hours of their formation. This is because IDL particles bind tightly to liver cells, which extract IDL cholesterol to make new VLDL and bile acids. The IDL not taken up by the liver is catabolized by the hepatic lipase, an enzyme bound to the proteoglycan on liver cells. Apo E dissociates from IDL as it is transformed to LDL. Apo B-100 is the sole protein of LDL.

Primarily, the liver takes up and degrades circulating cholesterol to bile acids, which are the end products of cholesterol metabolism. The uptake of cholesterol-containing particles is mediated by LDL receptors, which are present in high concentrations on hepatocytes. The LDL receptor binds both apo E and apo B-100 and is responsible for binding and removing both IDL and LDL from the circulation. In addition, remnant receptors are responsible for clearing chylomicrons and VLDL remnants *i.e.*, IDL). However, the affinity of apo E for the LDL receptor is greater than that of apo B-100. As a result, the LDL particles have a much longer circulating life span than IDL particles; LDL circulates for an average of two and a half days before binding to the LDL receptors in the liver and other tissues. High serum levels of LDL, the “bad” cholesterol, are positively associated with coronary heart disease. For example, in atherosclerosis, cholesterol derived from circulating LDL accumulates in the walls of arteries. This accumulation forms bulky plaques that inhibit the flow of blood until a clot eventually forms, obstructing an artery and causing a heart attack or stroke.

Ultimately, the amount of intracellular cholesterol liberated from the LDL controls cellular cholesterol metabolism. The accumulation of cellular cholesterol derived from VLDL and LDL controls three processes. First, it reduces the cell’s ability to make its own cholesterol by turning off the synthesis of HMGCoA reductase, a key enzyme in the

cholesterol biosynthetic pathway. Second, the incoming LDL-derived cholesterol promotes storage of cholesterol by the action of cholesterol acyltransferase (“ACAT”), the cellular enzyme that converts cholesterol into cholesteryl esters that are deposited in storage droplets. Third, the accumulation of cholesterol within the cell drives a feedback mechanism that inhibits cellular synthesis of new LDL receptors. Cells, therefore, adjust their complement of LDL receptors so that enough cholesterol is brought in to meet their metabolic needs, without overloading (for a review, see Brown & Goldstein, In, The Pharmacological Basis Of Therapeutics, 8th Ed., Goodman & Gilman, Pergamon Press, New York, 1990, Ch. 36, pp. 874-896).

High levels of apo B-containing lipoproteins can be trapped in the subendothelial space of an artery and undergo oxidation. The oxidized lipoprotein is recognized by scavenger receptors on macrophages. Binding of oxidized lipoprotein to the scavenger receptors can enrich the macrophages with cholesterol and cholesteryl esters independently of the LDL receptor. Macrophages can also produce cholesteryl esters by the action of ACAT. LDL can also be complexed to a high molecular weight glycoprotein called apolipoprotein(a), also known as apo(a), through a disulfide bridge. The LDL-apo(a) complex is known as Lipoprotein(a) or Lp(a). Elevated levels of Lp(a) are detrimental, having been associated with atherosclerosis, coronary heart disease, myocardial infarction, stroke, cerebral infarction, and restenosis following angioplasty.

2.2 Reverse Cholesterol Transport

Peripheral (non-hepatic) cells predominantly obtain their cholesterol from a combination of local synthesis and uptake of preformed sterol from VLDL and LDL. Cells expressing scavenger receptors, such as macrophages and smooth muscle cells, can also obtain cholesterol from oxidized apo B-containing lipoproteins. In contrast, reverse cholesterol transport (RCT) is the pathway by which peripheral cell cholesterol can be returned to the liver for recycling to extrahepatic tissues, hepatic storage, or excretion into the intestine in bile. The RCT pathway represents the only means of eliminating cholesterol from most extrahepatic tissues and is crucial to maintenance of the structure and function of most cells in the body.

The enzyme in blood involved in the RCT pathway, lecithin:cholesterol acyltransferase (LCAT), converts cell-derived cholesterol to cholesteryl esters, which are sequestered in HDL destined for removal. LCAT is produced mainly in the liver and circulates in plasma associated with the HDL fraction. Cholesterol ester transfer protein (CETP) and another lipid transfer protein, phospholipid transfer protein (PLTP), contribute

to further remodeling the circulating HDL population (see for example Bruce *et al.*, 1998, *Annu. Rev. Nutr.* 18:297-330). PLTP supplies lecithin to HDL, and CETP can move cholesteryl ester made by LCAT to other lipoproteins, particularly apoB-containing lipoproteins, such as VLDL. HDL triglyceride can be catabolized by the extracellular hepatic triglyceride lipase, and lipoprotein cholesterol is removed by the liver via several mechanisms.

Each HDL particle contains at least one molecule, and usually two to four molecules, of apolipoprotein (apo A-I). Apo A-I is synthesized by the liver and small intestine as preproapolipoprotein which is secreted as a proprotein that is rapidly cleaved to generate a mature polypeptide having 243 amino acid residues. Apo A-I consists mainly of a 22 amino acid repeating segment, spaced with helix-breaking proline residues. Apo A-I forms three types of stable structures with lipids: small, lipid-poor complexes referred to as pre-beta-1 HDL; flattened discoidal particles, referred to as pre-beta-2 HDL, which contain only polar lipids (*e.g.*, phospholipid and cholesterol); and spherical particles containing both polar and nonpolar lipids, referred to as spherical or mature HDL (HDL₃ and HDL₂). Most HDL in the circulating population contains both apo A-I and apo A-II, a second major HDL protein. This apo A-I- and apo A-II-containing fraction is referred to herein as the AI/AII-HDL fraction of HDL. But the fraction of HDL containing only apo A-I, referred to herein as the AI-HDL fraction, appears to be more effective in RCT. Certain epidemiologic studies support the hypothesis that the AI-HDL fraction is antiatherogenic (Parra *et al.*, 1992, *Arterioscler. Thromb.* 12:701-707; Decossin *et al.*, 1997, *Eur. J. Clin. Invest.* 27:299-307).

Although the mechanism for cholesterol transfer from the cell surface is unknown, it is believed that the lipid-poor complex, pre-beta-1 HDL, is the preferred acceptor for cholesterol transferred from peripheral tissue involved in RCT. Cholesterol newly transferred to pre-beta-1 HDL from the cell surface rapidly appears in the discoidal pre-beta-2 HDL. PLTP may increase the rate of disc formation (Lagrost *et al.*, 1996, *J. Biol. Chem.* 271:19058-19065), but data indicating a role for PLTP in RCT is lacking. LCAT reacts preferentially with discoidal and spherical HDL, transferring the 2-acyl group of lecithin or phosphatidylethanolamine to the free hydroxyl residue of fatty alcohols, particularly cholesterol, to generate cholesteryl esters (retained in the HDL) and lysolecithin. The LCAT reaction requires an apolipoprotein such as apo A-I or apo A-IV as an activator. ApoA-I is one of the natural cofactors for LCAT. The conversion of cholesterol to its HDL-sequestered ester prevents re-entry of cholesterol into the cell, resulting in the

ultimate removal of cellular cholesterol. Cholesteryl esters in the mature HDL particles of the AI-HDL fraction are removed by the liver and processed into bile more effectively than those derived from the AI/AII-HDL fraction. This may be due, in part, to the more effective binding of AI-HDL to the hepatocyte membrane. Several HDL receptor receptors have been identified, the most well characterized of which is the scavenger receptor class B, type I (SR-BI) (Acton *et al.*, 1996, *Science* 271:518-520). The SR-BI is expressed most abundantly in steroidogenic tissues (*e.g.*, the adrenals), and in the liver (Landshulz *et al.*, 1996, *J. Clin. Invest.* 98:984-995; Rigotti *et al.*, 1996, *J. Biol. Chem.* 271:33545-33549). Other proposed HDL receptors include HB1 and HB2 (Hidaka and Fidge, 1992, *Biochem J.* 15:161-7; Kurata *et al.*, 1998, *J. Atherosclerosis and Thrombosis* 4:112-7).

While there is a consensus that CETP is involved in the metabolism of VLDL- and LDL-derived lipids, its role in RCT remains controversial. However, changes in CETP activity or its acceptors, VLDL and LDL, play a role in “remodeling” the HDL population. For example, in the absence of CETP, the HDL becomes enlarged particles that are poorly removed from the circulation (for reviews on RCT and HDLs, see Fielding & Fielding, 1995, *J. Lipid Res.* 36:211-228; Barrans *et al.*, 1996, *Biochem. Biophys. Acta.* 1300:73-85; Hirano *et al.*, 1997, *Arterioscler. Thromb. Vasc. Biol.* 17:1053-1059).

2.3 Reverse transport of other lipids

HDL is not only involved in the reverse transport of cholesterol, but also plays a role in the reverse transport of other lipids, *i.e.*, the transport of lipids from cells, organs, and tissues to the liver for catabolism and excretion. Such lipids include sphingomyelin, oxidized lipids, and lysophosphatidylcholine. For example, Robins and Fasulo (1997, *J. Clin. Invest.* 99:380-384) have shown that HDL stimulates the transport of plant sterol by the liver into bile secretions.

2.4 Peroxisome Proliferator Activated Receptor Pathway

Peroxisome proliferators are a structurally diverse group of compounds that, when administered to rodents, elicit dramatic increases in the size and number of hepatic and renal peroxisomes, as well as concomitant increases in the capacity of peroxisomes to metabolize fatty acids via increased expression of the enzymes required for the β -oxidation cycle (Lazarow and Fujiki, 1985, *Ann. Rev. Cell Biol.* 1:489-530; Vamecq and Draye, 1989, *Essays Biochem.* 24:1115-225; and Nelali *et al.*, 1988, *Cancer Res.* 48:5316-5324). Chemicals included in this group are the fibrate class of hypolipidemic drugs, herbicides, and phthalate plasticizers (Reddy and Lalwani, 1983, *Crit. Rev. Toxicol.* 12:1-58).

Peroxisome proliferation can also be elicited by dietary or physiological factors, such as a high-fat diet and cold acclimatization.

Insight into the mechanism whereby peroxisome proliferators exert their pleiotropic effects was provided by the identification of a member of the nuclear hormone receptor superfamily activated by these chemicals (Isseman and Green, 1990, *Nature* 347:645-650). This receptor, termed peroxisome proliferator activated receptor α (PPAR α), was subsequently shown to be activated by a variety of medium and long-chain fatty acids. PPAR α activates transcription by binding to DNA sequence elements, termed peroxisome proliferator response elements (PPRE), in the form of a heterodimer with the retinoid X receptor (RXR). RXR is activated by 9-cis retinoic acid (*see* Kliewer *et al.*, 1992, *Nature* 358:771-774; Gearing *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90:1440-1444, Keller *et al.*, 1993, *Proc. Natl. Acad. Sci. USA* 90:2160-2164; Heyman *et al.*, 1992, *Cell* 68:397-406, and Levin *et al.*, 1992, *Nature* 355:359-361). Since the discovery of PPAR α , additional isoforms of PPAR have been identified, *e.g.*, PPAR β , PPAR γ and PPAR δ , which have similar functions and are similarly regulated.

PPREs have been identified in the enhancers of a number of gene-encoding proteins that regulate lipid metabolism. These proteins include the three enzymes required for peroxisomal β -oxidation of fatty acids; apolipoprotein A-I; medium-chain acyl-CoA dehydrogenase, a key enzyme in mitochondrial β -oxidation; and aP2, a lipid binding protein expressed exclusively in adipocytes (reviewed in Keller and Whali, 1993, *TEM*, 4:291-296; *see also* Staels and Auwerx, 1998, *Atherosclerosis* 137 Suppl:S19-23). The nature of the PPAR target genes coupled with the activation of PPARs by fatty acids and hypolipidemic drugs suggests a physiological role for the PPARs in lipid homeostasis.

Pioglitazone, an antidiabetic compound of the thiazolidinedione class, was reported to stimulate expression of a chimeric gene containing the enhancer/promoter of the lipid-binding protein aP2 upstream of the chloroamphenicol acetyl transferase reporter gene (Harris and Kletzien, 1994, *Mol. Pharmacol.* 45:439-445). Deletion analysis led to the identification of an approximately 30 bp region responsible for pioglitazone responsiveness. In an independent study, this 30 bp fragment was shown to contain a PPRE (Tontonoz *et al.*, 1994, *Nucleic Acids Res.* 22:5628-5634). Taken together, these studies suggested the possibility that the thiazolidinediones modulate gene expression at the transcriptional level through interactions with a PPAR and reinforce the concept of the interrelatedness of glucose and lipid metabolism.

2.5 Current Cholesterol Management Therapies

In the past two decades or so, the segregation of cholesterolemic compounds into HDL and LDL regulators and recognition of the desirability of decreasing blood levels of the latter has led to the development of a number of drugs. However, many of these drugs have undesirable side effects and/or are contraindicated in certain patients, particularly when administered in combination with other drugs.

Bile-acid-binding resins are a class of drugs that interrupt the recycling of bile acids from the intestine to the liver. Examples of bile-acid-binding resins are cholestyramine (QUESTRAN LIGHT, Bristol-Myers Squibb), and colestipol hydrochloride (COLESTID, Pharmacia & Upjohn Company). When taken orally, these positively charged resins bind to negatively charged bile acids in the intestine. Because the resins cannot be absorbed from the intestine, they are excreted, carrying the bile acids with them. The use of such resins, however, at best only lowers serum cholesterol levels by about 20%. Moreover, their use is associated with gastrointestinal side-effects, including constipation and certain vitamin deficiencies. Moreover, since the resins bind to drugs, other oral medications must be taken at least one hour before or four to six hours subsequent to ingestion of the resin, complicating heart patients' drug regimens.

The statins are inhibitors of cholesterol synthesis. Sometimes, the statins are used in combination therapy with bile-acid-binding resins. Lovastatin (MEVACOR, Merck & Co., Inc.), a natural product derived from a strain of *Aspergillus*; pravastatin (PRAVACHOL, Bristol-Myers Squibb Co.); and atorvastatin (LIPITOR, Warner Lambert) block cholesterol synthesis by inhibiting HMGCoA, the key enzyme involved in the cholesterol biosynthetic pathway. Lovastatin significantly reduces serum cholesterol and LDL-serum levels. It also slows progression of coronary atherosclerosis. However, serum HDL levels are only slightly increased following lovastatin administration. The mechanism of the LDL-lowering effect may involve both reduction of VLDL concentration and induction of cellular expression of LDL-receptor, leading to reduced production and/or increased catabolism of LDL. Side effects, including liver and kidney dysfunction are associated with the use of these drugs.

Niacin, also known as nicotinic acid, is a water-soluble vitamin B-complex used as a dietary supplement and antihyperlipidemic agent. Niacin diminishes production of VLDL and is effective at lowering LDL. It is used in combination with bile-acid-binding resins. Niacin can increase HDL when administered at therapeutically effective doses; however, its usefulness is limited by serious side effects.

Fibrates are a class of lipid-lowering drugs used to treat various forms of hyperlipidemia, elevated serum triglycerides, which may also be associated with hypercholesterolemia. Fibrates appear to reduce the VLDL fraction and modestly increase HDL; however, the effects of these drugs on serum cholesterol is variable. In the United States, fibrates have been approved for use as antilipidemic drugs, but have not received approval as hypercholesterolemia agents. For example, clofibrate (ATROMID-S, Wyeth-Ayerst Laboratories) is an antilipidemic agent that acts to lower serum triglycerides by reducing the VLDL fraction. Although ATROMID-S may reduce serum cholesterol levels in certain patient subpopulations, the biochemical response to the drug is variable, and is not always possible to predict which patients will obtain favorable results. ATROMID-S has not been shown to be effective for prevention of coronary heart disease. The chemically and pharmacologically related drug, gemfibrozil (LOPID, Parke-Davis), is a lipid regulating agent which moderately decreases serum triglycerides and VLDL cholesterol. LOPID also increases HDL cholesterol, particularly the HDL₂ and HDL₃ subfractions, as well as both the AI/AII-HDL fraction. However, the lipid response to LOPID is heterogeneous, especially among different patient populations. Moreover, while prevention of coronary heart disease was observed in male patients between the ages of 40 and 55 without history or symptoms of existing coronary heart disease, it is not clear to what extent these findings can be extrapolated to other patient populations (*e.g.*, women, older and younger males). Indeed, no efficacy was observed in patients with established coronary heart disease. Serious side-effects are associated with the use of fibrates, including toxicity; malignancy, particularly malignancy of gastrointestinal cancer; gallbladder disease; and an increased incidence in non-coronary mortality. These drugs are not indicated for the treatment of patients with high LDL or low HDL as their only lipid abnormality.

Oral estrogen replacement therapy may be considered for moderate hypercholesterolemia in post-menopausal women. However, increases in HDL may be accompanied with an increase in triglycerides. Estrogen treatment is, of course, limited to a specific patient population, postmenopausal women, and is associated with serious side effects, including induction of malignant neoplasms; gall bladder disease; thromboembolic disease; hepatic adenoma; elevated blood pressure; glucose intolerance; and hypercalcemia.

Long chain carboxylic acids, particularly long chain α,ω -dicarboxylic acids with distinctive substitution patterns, and their simple derivatives and salts, have been disclosed for treating atherosclerosis, obesity, and diabetes (See, *e.g.*, Bisgaier *et al.*, 1998, *J. Lipid*

Res. 39:17-30, and references cited therein; International Patent Publication WO 98/30530; U.S. Patent No. 4,689,344; International Patent Publication WO 99/00116; and U.S. Patent No. 5,756,344). However, some of these compounds, for example the α,ω -dicarboxylic acids substituted at their α,α' -carbons (U.S. Patent No. 3,773,946), while having serum triglyceride and serum cholesterol-lowering activities, have no value for treatment of obesity and hypercholesterolemia (U.S. Patent No. 4,689,344).

U.S. Patent No. 4,689,344 discloses $\beta,\beta,\beta',\beta'$ -tetrasubstituted- α,ω -alkanedioic acids that are optionally substituted at their $\alpha,\alpha,\alpha',\alpha'$ -positions, and alleges that they are useful for treating obesity, hyperlipidemia, and diabetes. According to this reference, both triglycerides and cholesterol are lowered significantly by compounds such as 3,3,14,14-tetramethylhexadecane-1,16-dioic acid. U.S. Patent No. 4,689,344 further discloses that the $\beta,\beta,\beta',\beta'$ -tetramethyl-alkanediols of U.S. Patent No. 3,930,024 also are not useful for treating hypercholesterolemia or obesity.

Other compounds are disclosed in U.S. Patent No. 4,711,896. In U.S. Patent No. 5,756,544, α,ω -dicarboxylic acid-terminated dialkane ethers are disclosed to have activity in lowering certain plasma lipids, including Lp(a), triglycerides, VLDL-cholesterol, and LDL-cholesterol, in animals, and elevating others, such as HDL-cholesterol. The compounds are also stated to increase insulin sensitivity. In U.S. Patent No. 4,613,593, phosphates of dolichol, a polyprenol isolated from swine liver, are stated to be useful in regenerating liver tissue, and in treating hyperuricuria, hyperlipemia, diabetes, and hepatic diseases in general.

U.S. Patent No. 4,287,200 discloses azolidinedione derivatives with anti-diabetic, hypolipidemic, and anti-hypertensive properties. However, the administration of these compounds to patients can produce side effects such as bone marrow depression, and both liver and cardiac cytotoxicity. Further, the compounds disclosed by U.S. Patent No. 4,287,200 stimulate weight gain in obese patients.

It is clear that none of the commercially available cholesterol management drugs has a general utility in regulating lipid, lipoprotein, insulin and glucose levels in the blood. Thus, compounds that have one or more of these utilities are clearly needed. Further, there is a clear need to develop safer drugs that are efficacious at lowering serum cholesterol, increasing HDL serum levels, preventing coronary heart disease, and/or treating existing disease such as atherosclerosis, obesity, diabetes, and other diseases that are affected by lipid metabolism and/or lipid levels. There is also a clear need to develop drugs that may be used with other lipid-altering treatment regimens in a synergistic manner. There is still a

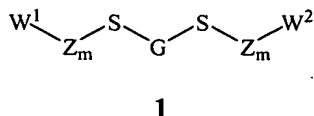
further need to provide useful therapeutic agents whose solubility and Hydrophile/Lipophile Balance (HLB) can be readily varied.

Citation or identification of any reference in Section 2 of this application is not an admission that such reference is available as prior art to the present invention.

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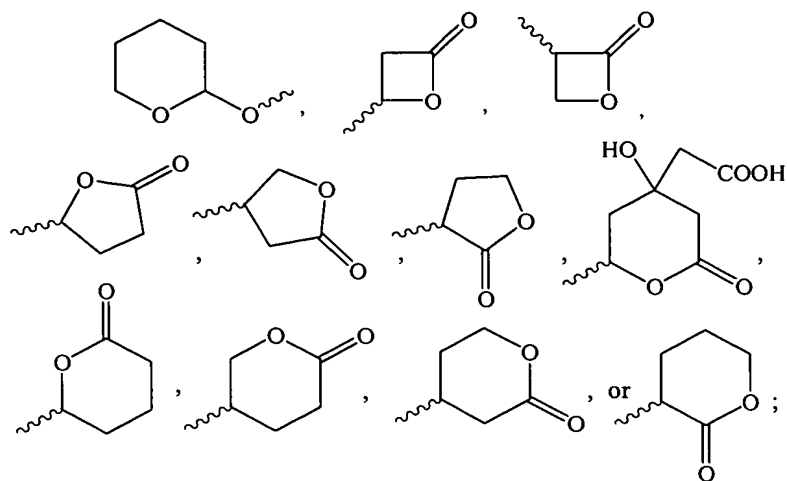
3. Summary of The Invention

In one embodiment, the invention relates to a compound of the formula 1:

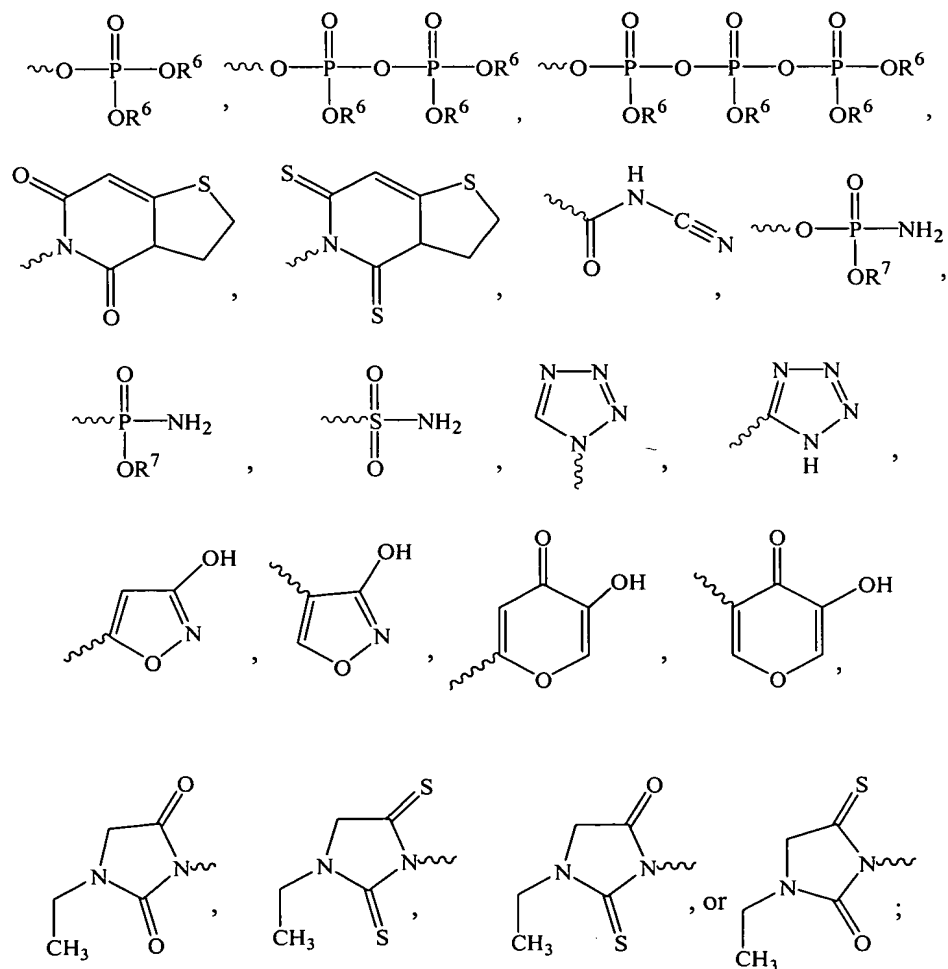


10 or a pharmaceutically acceptable salt, hydrate, solvate, or a mixture thereof, wherein

- (a) each occurrence of Z is independently CH₂, CH=CH, or phenyl, where each occurrence of m is independently an integer ranging from 1 to 9, but when Z is phenyl then its associated m is 1;
- (b) G is (CH₂)_x, where x is 2, 3, or 4, CH₂CH=CHCH₂, CH=CH, CH₂-phenyl-CH₂, or phenyl;
- (c) W¹ and W² are independently L, V, C(R¹)(R²)-(CH₂)_c-C(R³)(R⁴)-(CH₂)_n-Y, or C(R¹)(R²)-(CH₂)_c-V where c is 1 or 2 and n is an integer ranging from 0 to 4;
- (d) each occurrence of R¹ or R² is independently (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, phenyl, or benzyl or when one or both of W¹ and W² is C(R¹)(R²)-(CH₂)_c-C(R³)(R⁴)-Y, then R¹ and R² can both be H to form a methylene group; or R¹ and R² and the carbon to which they are both attached are taken together to form a (C₃-C₇)cycloalkyl group;
- (e) each occurrence of R³ or R⁴ is independently H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, (C₁-C₆)alkoxy, phenyl, benzyl, Cl, Br, CN, NO₂, or CF₃, with the proviso that when R¹ and R² are both H, then one of R³ and R⁴ is not H;
- (f) L is C(R¹)(R²)-(CH₂)_n-Y; or R³ and R⁴ and the carbon to which they are both attached are taken together to form a (C₃-C₇)cycloalkyl group;
- (g) V is



(h) each occurrence of Y is independently (C₁-C₆)alkyl, OH, COOH, CHO, COOR⁵, SO₃H,



where

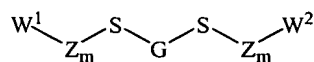
(i) R^5 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, (C_1-C_6) alkoxy, or phenyl groups,

5 (ii) each occurrence of R^6 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl and is unsubstituted or substituted with one or two halo, OH, C_1-C_6 alkoxy, or phenyl groups; and

(iii) each occurrence of R^7 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl.

In another embodiment, the invention encompasses compounds of formula

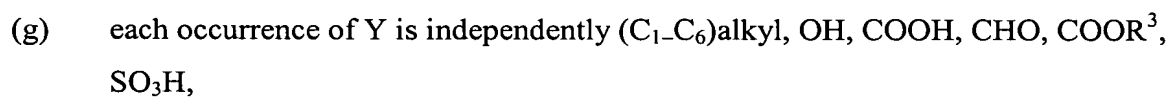
10 **Ia:**



Ia

or a pharmaceutically acceptable salt, hydrate, solvate, or a mixture thereof, wherein

- 15 (a) each occurrence of Z is independently CH_2 or $CH=CH$, wherein each occurrence of m is independently an integer ranging from 1 to 9;
- (b) G is $(CH_2)_x$, $CH_2CH=CHCH_2$, or $CH=CH$, where x is 2, 3, or 4;
- (c) W^1 and W^2 are independently L, V, or $C(R^1)(R^2)-(CH_2)_c-V$, where c is 1 or 2;
- 20 (d) each occurrence of R^1 and R^2 is independently (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, benzyl, or R^1 and R^2 and the carbon to which they are both attached are taken together to form a (C_3-C_7) cycloalkyl group;
- (e) L is $C(R^1)(R^2)-(CH_2)_n-Y$, where n is an integer ranging from 0 to 4;
- (f) V is



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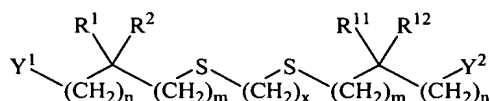
(i) R^3 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, (C_1-C_6) alkoxy, or phenyl groups,

5 (ii) each occurrence of R^4 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl and is unsubstituted or substituted with one or two halo, OH, C_1-C_6 alkoxy, or phenyl groups; and

(iii) each occurrence of R^5 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl.

10 Preferably, in formula **Ia** each occurrence of Y is independently OH, $COOR^3$, or COOH.

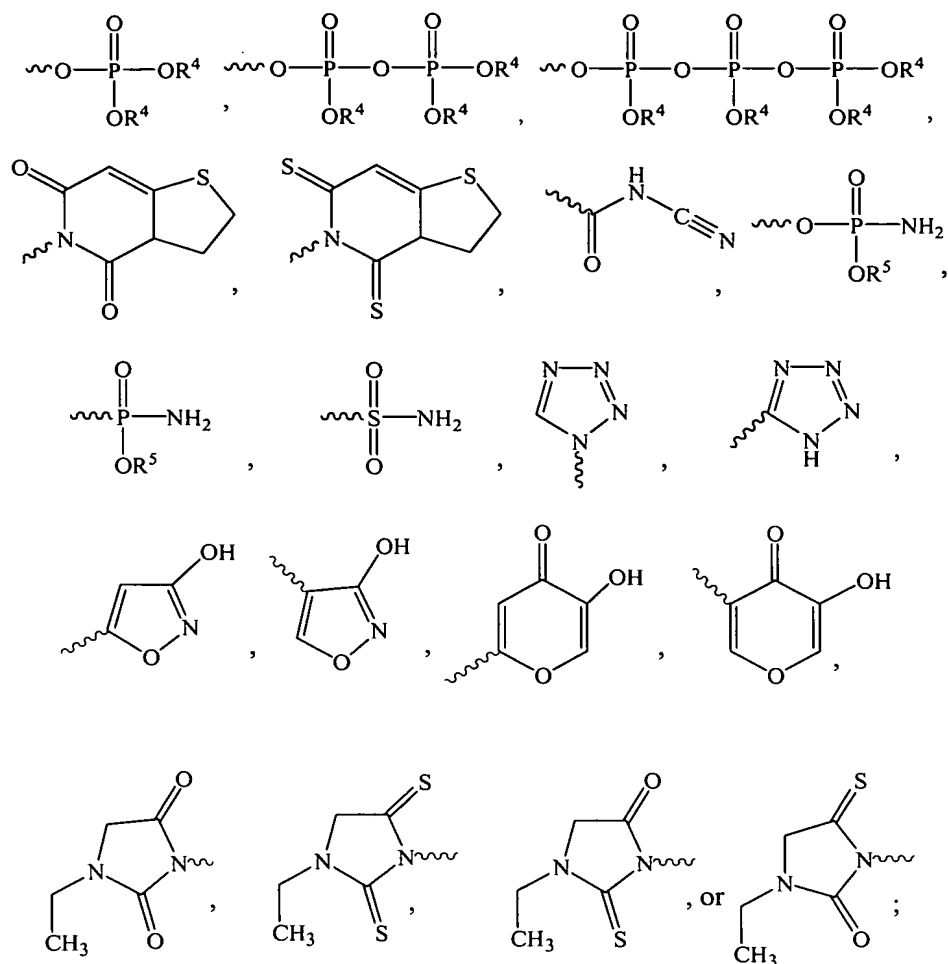
In yet another embodiment, the invention encompasses compounds of formula **Ib**



Ib

or a pharmaceutically acceptable salt, hydrate, solvate, or a mixture thereof, wherein:

- 15 (a) each occurrence of m is independently an integer ranging from 1 to 9;
- (b) x is 2, 3, or 4;
- (c) each occurrence of n is independently an integer ranging from 0 to 4;
- (d) each occurrence of R^1 and R^2 is independently (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, benzyl. or R^1 and R^2 and the carbon to which they are both
20 attached are taken together to form a (C_3-C_7) cycloalkyl group;
- (e) each occurrence of R^{11} and R^{12} is independently (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, benzyl. or R^{11} and R^{12} and the carbon to which they are both attached are taken together to form a (C_3-C_7) cycloalkyl group;
- 25 (e) each occurrence of Y is independently (C_1-C_6) alkyl, OH, COOH, CHO, $COOR^3$, SO_3H ,



where

5 (i) R^3 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, (C_1-C_6) alkoxy, or phenyl groups,

10 (ii) each occurrence of R^4 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl and is unsubstituted or substituted with one or two halo, OH, C_1-C_6 alkoxy, or phenyl groups; and

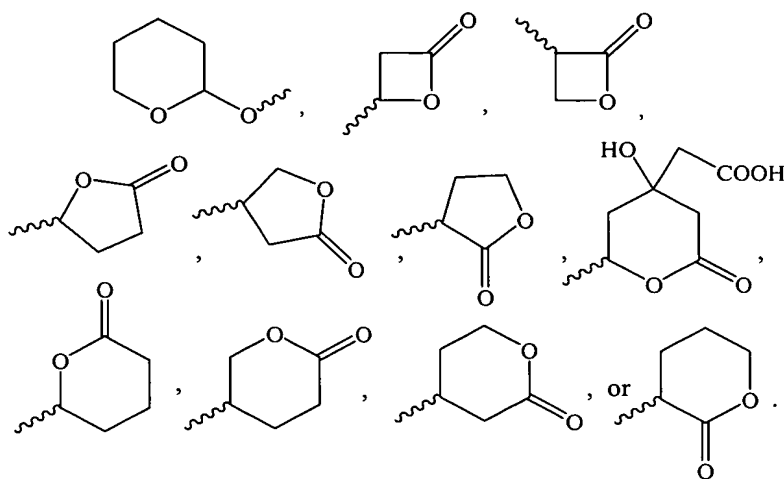
(iii) each occurrence of R^5 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl.

Preferably in formula **Ib**, each occurrence of Y is independently OH, $COOR^3$, or COOH.

$$\text{V} - (\text{CH}_2)_m - \text{S} - (\text{CH}_2)_x - \text{S} - (\text{CH}_2)_m - \text{V}$$

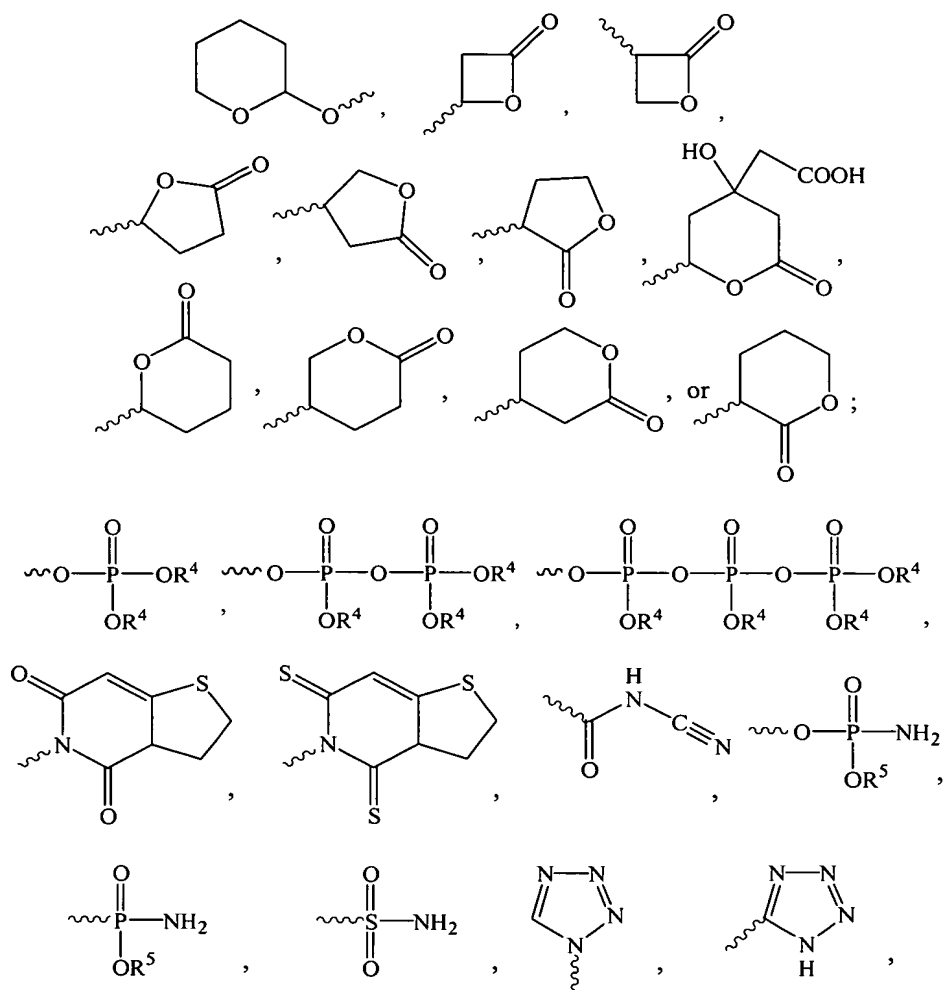
Ic

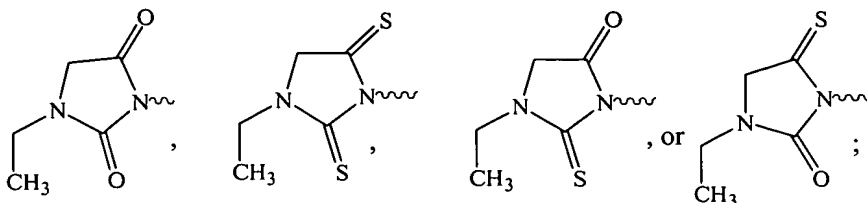
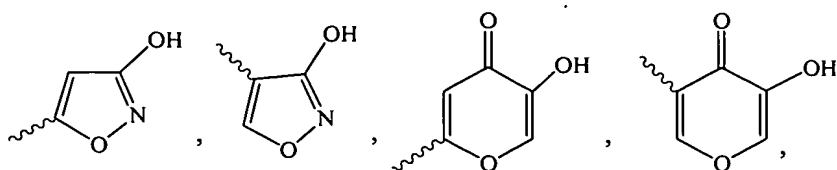
- each occurrence of m is an independent integer ranging from 1 to 9;
- x is 2, 3, or 4;
- V is


$$\begin{array}{c} \text{R}^1 \quad \text{R}^2 \quad \text{R}^{11} \quad \text{R}^{12} \\ \diagup \quad \diagdown \quad \diagup \quad \diagdown \\ \text{W}^1 - (\text{CH}_2)_n - (\text{CH}_2)_m - \text{S} - (\text{CH}_2)_m - (\text{CH}_2)_n - \text{W}^2 \\ \text{II} \end{array}$$

15 (a) each occurrence of R¹ or R² is independently (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, benzyl, phenyl, or R¹ or R² and the carbon to which they are both attached are taken together to form (C₃-C₇)cycloalkyl group;

- (b) each occurrence of R^{11} or R^{12} is independently (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, benzylyl, phenyl, or R^{11} and R^{12} and the carbon to which they are both attached are taken together to form (C_3-C_7) cycloalkyl group;
- (c) each occurrence of n is independently an integer ranging from 0 to 6;
- 5 (d) each occurrence of m is independently an integer ranging from 1 to 8;
- (e) W^1 and W^2 are independently (C_1-C_6) alkyl, CH_2OH , $C(O)OH$, CHO , $OC(O)R^3$, $C(O)OR^3$, SO_3H ,





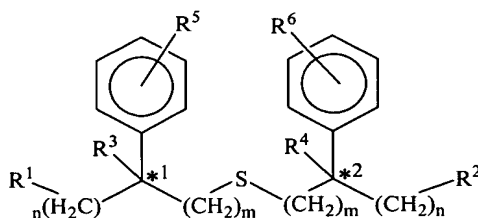
where

(i) R^3 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, (C_1-C_6) alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl and is unsubstituted or substituted with one or two halo, OH, C_1-C_6 alkoxy, or phenyl groups; and

(iii) each occurrence of R^5 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl.

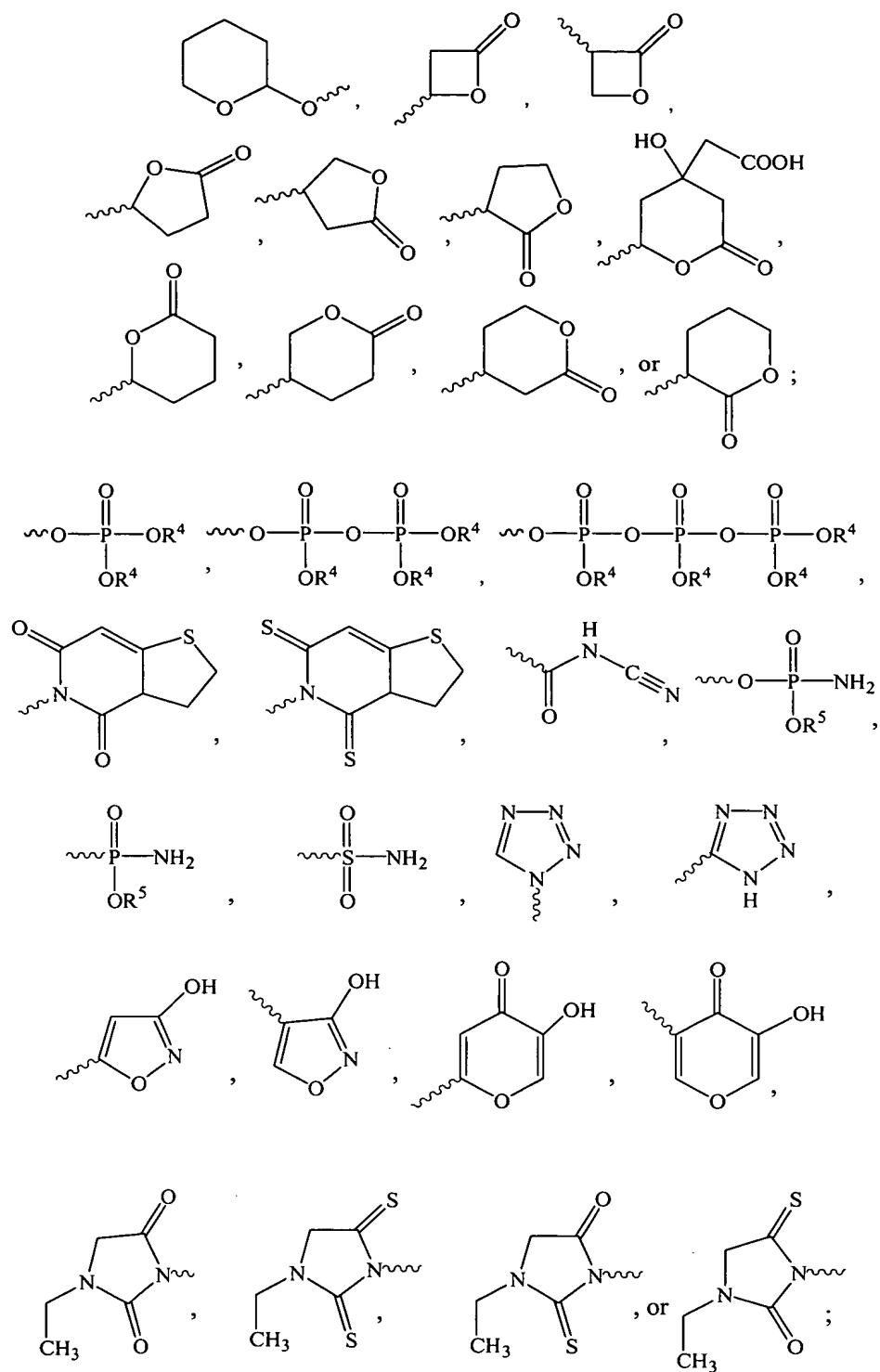
In another embodiment, the invention encompasses compounds of formula **IIa**:



IIa

or a pharmaceutically acceptable salt, hydrate, solvate, or a mixture thereof, wherein

(a) R^1 and R^2 are (C_1-C_6) alkyl, OH, COOH, CHO, COOR⁷, SO₃H,



5

where

(i) R^7 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, (C_1-C_6) alkoxy, or phenyl groups,

(ii) each occurrence of R^8 is independently H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl and is unsubstituted or substituted with one or two halo, OH, C₁-C₆ alkoxy, or phenyl groups,

5 (iii) each occurrence of R^9 is independently H, (C₁-C₆)alkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl;

(b) R^3 and R^4 are (C₁-C₆)alkyl, (C₂-C₆)alkenyl, (C₂-C₆)alkynyl, phenyl, or benzyl;

(c) R^5 and R^6 are H, halogen, (C₁-C₄)alkyl, (C₁-C₄)alkoxy, (C₆)aryloxy, CN, or NO₂, N(R^5)₂ where R^5 is H, (C₁-C₄) alkyl, phenyl, or benzyl;

(d) each occurrence of m is independently an integer ranging from 1 to 5;

10 (e) each occurrence of n is independently an integer ranging from 0 to 4; and

(f) *¹ and *² represent independent chiral-carbon centers, wherein each center may independently be R or S.

Preferred compounds of formula **IIa** are those wherein each occurrence of R^1 and R^2 is independently OH, COOR⁷, or COOH.

15 Other preferred compounds of formula **IIa** are those wherein m is 0.

Other preferred compounds of formula **IIa** are those wherein m is 1.

Other preferred compounds of formula **IIa** are those wherein R^1 and/or R^2 is C(O)OH or CH₂OH.

20 Other preferred compounds of formula **IIa** are those wherein R^3 and R^4 are each independently (C₁-C₆) alkyl.

Other preferred compounds of formula **IIa** are those wherein R^3 and R^4 are each methyl.

Other preferred compounds of formula **IIa** are those wherein *¹ is of the stereochemical configuration R or substantially R.

25 Other preferred compounds of formula **IIa** are those wherein *¹ is of the stereochemical configuration S or substantially S.

Other preferred compounds of formula **IIa** are those wherein *² is of the stereochemical configuration R or substantially R.

30 Other preferred compounds of formula **IIa** are those wherein *² is of the stereochemical configuration S or substantially S.

stereochemical configuration S or substantially S.

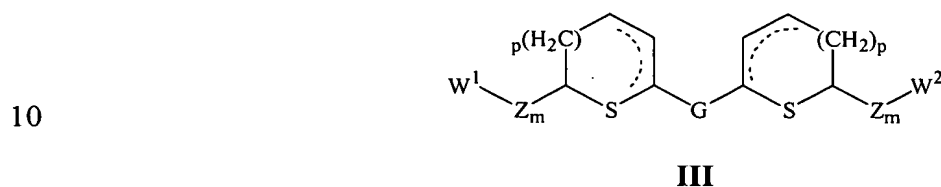
In a particular embodiment, compounds of formula **IIa** are those wherein $*^1$ $*^2$ are of the stereochemical configuration (S^1, S^2) or substantially (S^1, S^2).

In another particular embodiment, compounds of formula **IIa** are those wherein $*^1$ $*^2$ are of the stereochemical configuration (S^1, R^2) or substantially (S^1, R^2).

5 In another particular embodiment, compounds of formula **IIa** are those wherein $*^1$ $*^2$ are of the stereochemical configuration (R^1, R^2) or substantially (R^1, R^2).

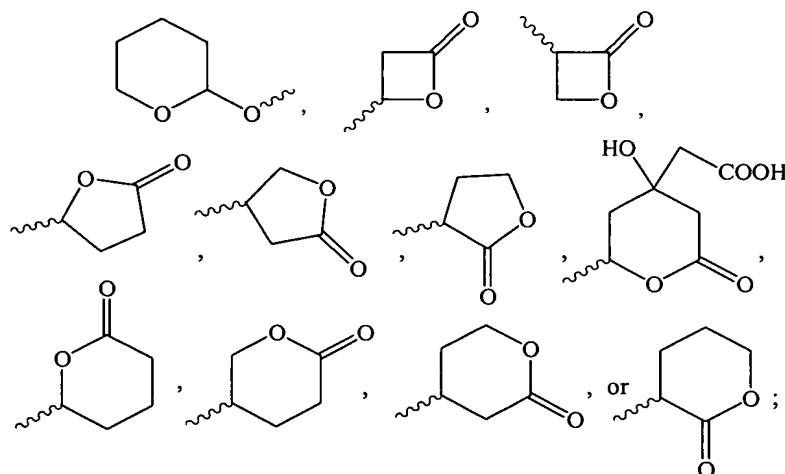
In another particular embodiment, compounds of formula **IIa** are those wherein $*^1$ $*^2$ are of the stereochemical configuration (R^1, S^2) or substantially (R^1, S^2).

In yet another embodiment, the invention encompasses compounds of formula **III**



or a pharmaceutically acceptable salt, hydrate, solvate, or a mixture thereof, wherein:

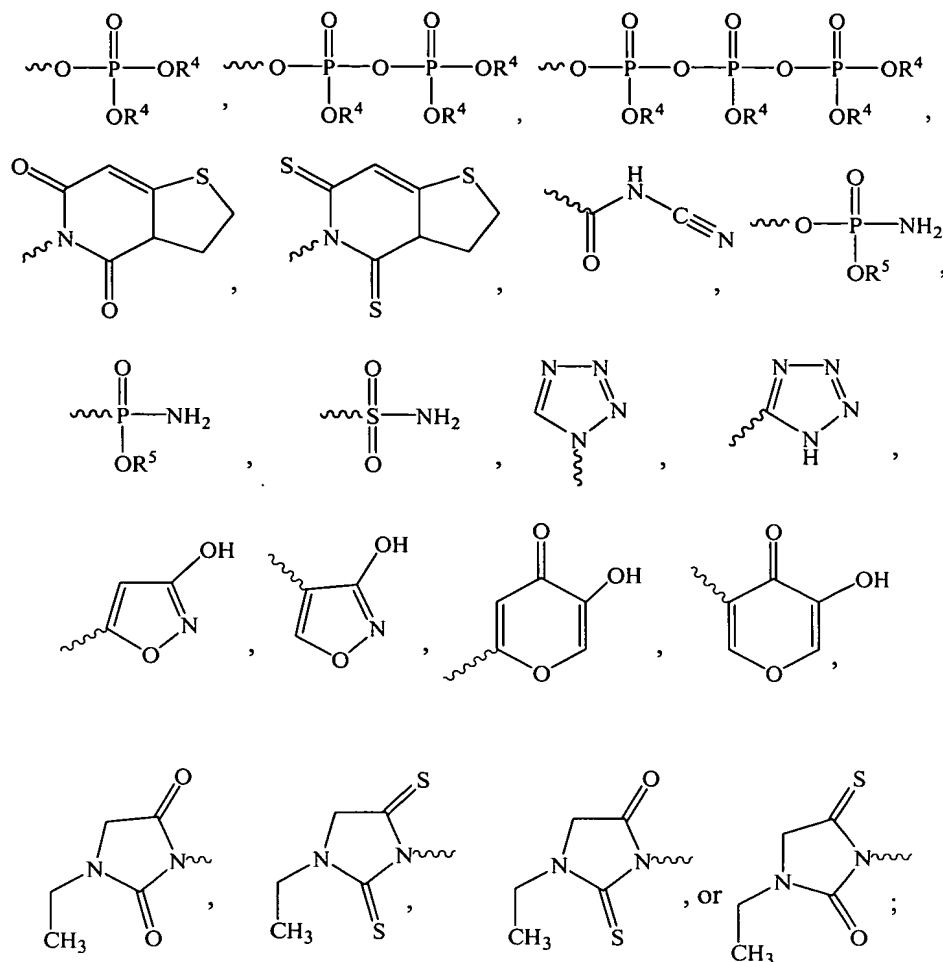
- 15
- (a) each occurrence of Z is independently CH_2 , $CH=CH$, or phenyl, where each occurrence of m is independently an integer ranging from 1 to 5, but when Z is phenyl then its associated m is 1;
 - (b) G is $(CH_2)_x$, $CH_2CH=CHCH_2$, $CH=CH$, CH_2 -phenyl- CH_2 , or phenyl, where x is an integer ranging from 1 to 4;
 - (c) W^1 and W^2 are independently $C(R^1)(R^2)-(CH_2)_n-Y$;



- 20 (d) each occurrence of n is independently an integer ranging from 0 to 4;

(e) R^1 and R^2 are independently (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl or R^1 and R^2 are both H;

(f) Y is (C_1-C_6) alkyl, OH, COOH, CHO, COOR³, SO₃H,



5

where

(i) R^3 is (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, phenyl, or benzyl and is unsubstituted or substituted with one or more halo, OH, (C_1-C_6) alkoxy, or phenyl groups,

(ii) each occurrence of R^4 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl and is unsubstituted or substituted with one or two halo, OH, C_1-C_6 alkoxy, or phenyl groups,

(iii) each occurrence of R^5 is independently H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, or (C_2-C_6) alkynyl; and

10

15

(g) each occurrence of p is independently 2 or 3 where the broken line represents an optional presence of one or more additional carbon-carbon bonds that when present complete one or more carbon-carbon double bonds.

Preferably in formula **III**, each occurrence of W^1 and W^2 is an independent
5 $C(R^1)(R^2)-(CH_2)_n-Y$ group and each occurrence of Y is independently OH, $COOR^3$, or COOH.

In another embodiment, the compounds of the invention are of formula **IIIa**, wherein the dashed line of compound **III** is removed, and therefore the rings are saturated.

The compounds of the invention are useful in medical applications for treating or
10 preventing aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis,
15 Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (*e.g.*, Syndrome X), a thrombotic disorder, inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (*e.g.*, Crohn's Disease, ulcerative colitis), arthritis (*e.g.*, rheumatoid arthritis, osteoarthritis),
20 autoimmune disease (*e.g.*, systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism. As used herein, the phrase "compounds of the invention" means, collectively, the compounds of formulas **I**, **II**, and **III** and
25 pharmaceutically acceptable salts, hydrates, solvates, and clathrates, enantiomers, diastereomer, racemates or mixtures of stereoisomers thereof. Compounds of formula **I** encompass subgroup formulas **Ia Ib**, and **Ic**. Compounds of formula **II** encompass the subgroup of formula **IIa**, and compounds of formula **III** encompass subgroup of formula **IIIa**. Thus, "compound of the invention" collectively means compound of formulas **I**, **Ia**,
30 **Ib**, **Ic**, **II**, **IIa**, **III**, and **IIIa** and pharmaceutically acceptable salts, hydrates, solvates, clathrates, enantiomers, diastereomers, racemates or mixtures of stereoisomers thereof. The compounds of the invention are identified herein by their chemical structure and/or chemical name. Where a compound is referred to by both a chemical structure and a

chemical name, and the chemical structure and chemical name conflict, the chemical structure is determinative of the compound's identity.

The present invention further provides pharmaceutical compositions comprising one or more compounds of the invention and a pharmaceutically acceptable vehicle, excipient, or diluent. A pharmaceutically acceptable vehicle can comprise a carrier, excipient, diluent, or a mixture thereof. These pharmaceutical compositions are useful for treating or preventing aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (*e.g.*, Syndrome X), a thrombotic disorder, inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (*e.g.*, Crohn's Disease, ulcerative colitis), arthritis (*e.g.*, rheumatoid arthritis, osteoarthritis), autoimmune disease (*e.g.*, systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism. These pharmaceutical composition are also useful for reducing the fat content of meat in livestock and reducing the cholesterol content of eggs.

The present invention provides a method for treating or preventing a aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (*e.g.*, Syndrome X), a thrombotic disorder, inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (*e.g.*, Crohn's Disease, ulcerative colitis), arthritis (*e.g.*, rheumatoid arthritis, osteoarthritis), autoimmune disease (*e.g.*, systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain:

polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism, comprising administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of the invention or a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable vehicle, excipient, or diluent.

The invention also encompasses a method for inhibited hepatic fatty acid and sterol synthesis comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the invention or a pharmaceutical composition comprising a compound of the invention and a pharmaceutically acceptable vehicle, excipient, or diluent.

The invention also encompasses a method of treating or preventing a disease or disorder that is capable of being treated or prevented by increasing HDL levels, which comprises administering to a patient in need of such treatment or prevention a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable vehicle, excipient, or diluent.

The invention also encompasses a method of treating or preventing a disease or disorder that is capable of being treated or prevented by lowering LDL levels, which comprises administering to such patient in need of such treatment or prevention a therapeutically effective amount of a compound of the invention and a pharmaceutically acceptable vehicle, excipient, or diluent.

The compounds of the invention favorably alter lipid metabolism in animal models of dyslipidemia at least in part by enhancing oxidation of fatty acids through the ACC/malonyl-CoA/CPT-I regulatory axis and therefore the invention also encompasses methods of treatment or prevention of metabolic syndrome disorders.

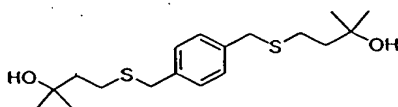
Thus, the compounds of the present invention are useful for the treatment of vascular disease, such as cardiovascular disease, stroke, and peripheral vascular disease; dyslipidemia; dyslipoproteinemia; a disorder of glucose metabolism; Alzheimer's Disease; Syndrome X; a peroxisome proliferator activated receptor-associated disorder; septicemia; a thrombotic disorder; obesity; pancreatitis; hypertension; renal disease; cancer; inflammation; inflammatory muscle diseases, such as polymyalgia rheumatica, polymyositis, and fibrositis; impotence; gastrointestinal disease; irritable bowel syndrome; inflammatory bowel disease; inflammatory disorders, such as asthma, vasculitis, ulcerative colitis, Crohn's disease, Kawasaki disease, Wegener's granulomatosis, (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and autoimmune chronic hepatitis; arthritis, such as rheumatoid arthritis, juvenile rheumatoid arthritis, and osteoarthritis;

osteoporosis, soft tissue rheumatism, such as tendonitis; bursitis; autoimmune disease, such as systemic lupus and erythematosus; scleroderma; ankylosing spondylitis; gout; pseudogout; non-insulin dependent diabetes mellitus; polycystic ovarian disease; hyperlipidemias, such as familial hypercholesterolemia (FH), familial combined

5 hyperlipidemia (FCH); lipoprotein lipase deficiencies, such as hypertriglyceridemia, hypoalphalipoproteinemia, and hypercholesterolemia; lipoprotein abnormalities associated with diabetes; lipoprotein abnormalities associated with obesity; and lipoprotein abnormalities associated with Alzheimer's Disease. The compounds and compositions of the invention are useful for treatment or prevention of high levels of blood triglycerides,

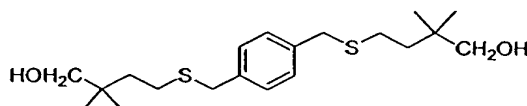
10 high levels of low density lipoprotein cholesterol, high levels of apolipoprotein B, high levels of lipoprotein Lp(a) cholesterol, high levels of very low density lipoprotein cholesterol, high levels of fibrinogen, high levels of insulin, high levels of glucose, and low

levels of high density lipoprotein cholesterol. The compounds and compositions of the invention also have utility for treatment of NIDDM without increasing weight gain. Some illustrative compounds of the invention are listed in Table I below.



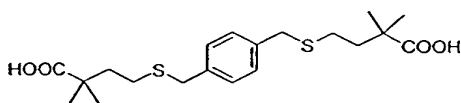
I-1

4-[4-(3-Hydroxy-3-methyl-butylsulfanylmethyl)-benzylsulfanyl]-2-methyl-butan-2-ol



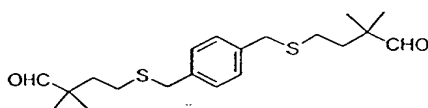
I-2

4-[4-(4-Hydroxy-3,3-dimethyl-butylsulfanylmethyl)-benzylsulfanyl]-2,2-dimethyl-butan-1-ol



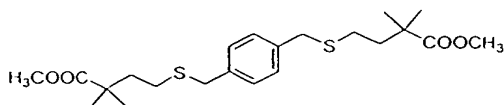
I-3

4-[4-(3-Carboxy-3-methyl-butylsulfanylmethyl)-benzylsulfanyl]-2,2-dimethyl-butyric acid



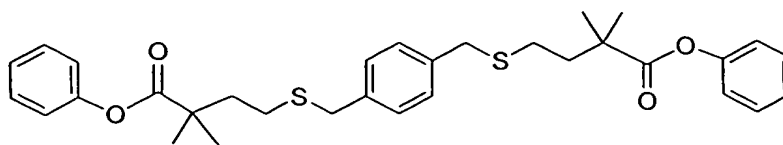
I-4

4-[4-(3,3-Dimethyl-4-oxo-butylsulfanylmethyl)-benzylsulfanyl]-2,2-dimethyl-butyraldehyde



I-5

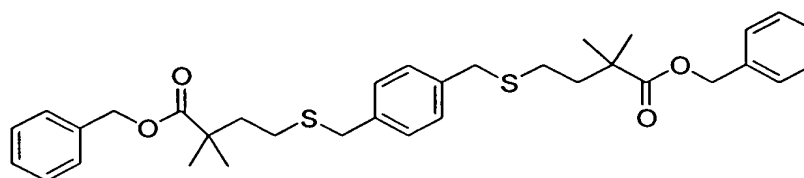
4-[4-(3-Methoxycarbonyl-3-methyl-butylsulfanylmethyl)-benzylsulfanyl]-2,2-dimethyl-butyric acid methyl ester



5

I-6

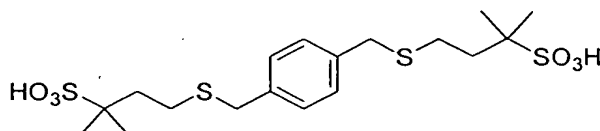
2,2-Dimethyl-4-[4-(3-methyl-3-phenoxybutylsulfanylmethyl)-benzylsulfanyl]-
butyric acid phenyl ester



10

I-7

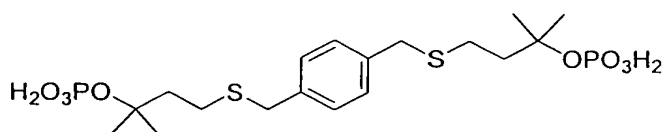
4-[4-(3-Benzoyloxycarbonyl-3-methyl-butylsulfanylmethyl)-benzylsulfanyl]-2,2-dimethyl-
butyric acid benzyl ester



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I-8

2-Methyl-4-[4-(3-methyl-3-sulfo-butylsulfanylmethyl)-benzylsulfanyl]-butane-2-sulfonic
acid

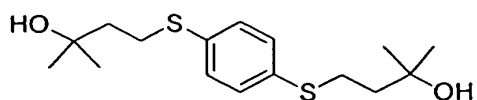


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I-9

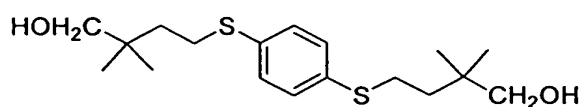
Phosphoric acid mono-{1,1-dimethyl-3-[4-(3-methyl-3-phosphonooxy-
butylsulfanylmethyl)-benzylsulfanyl]-propyl} ester

35



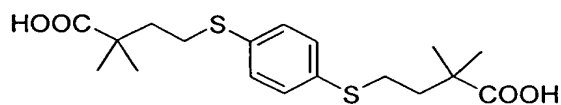
I-10

5 4-[4-(3-Hydroxy-3-methyl-butylsulfanyl)-phenylsulfanyl]-2-methyl-butan-2-ol



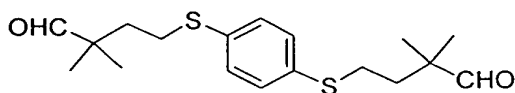
I-11

10 4-[4-(4-Hydroxy-3,3-dimethyl-butylsulfanyl)-phenylsulfanyl]-2,2-dimethyl-butan-1-ol



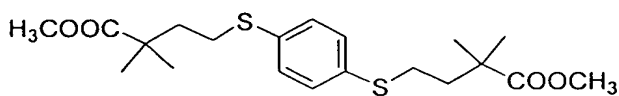
I-12

15 4-[4-(3-Carboxy-3-methyl-butylsulfanyl)-phenylsulfanyl]-2,2-dimethyl-butyric acid



I-13

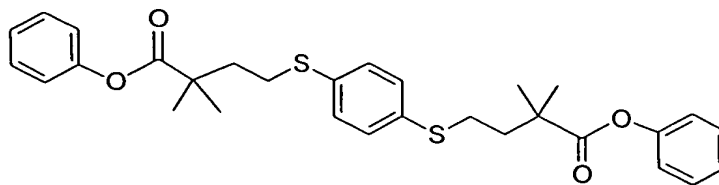
20 4-[4-(3,3-Dimethyl-4-oxo-butylsulfanyl)-phenylsulfanyl]-2,2-dimethyl-butyraldehyde



I-14

30 4-[4-(3-Methoxycarbonyl-3-methyl-butylsulfanyl)-phenylsulfanyl]-2,2-dimethyl-butyric
acid methyl ester

35

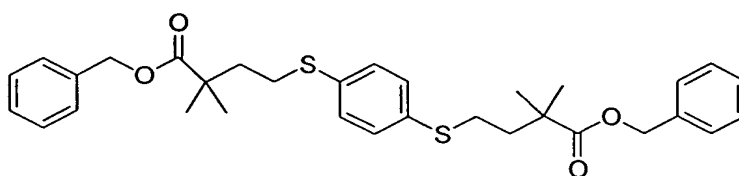


5

I-15

2,2-Dimethyl-4-[4-(3-methyl-3-phenoxybutylsulfanyl)-phenylsulfanyl]-butyric
acid phenyl ester

10

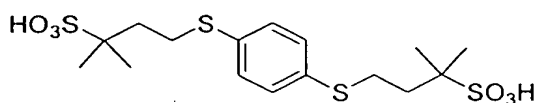


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I-16

4-[4-(3-Benzoyloxycarbonyl-3-methyl-butylsulfanyl)-phenylsulfanyl]-2,2-dimethyl-butyl
acid benzyl ester

20

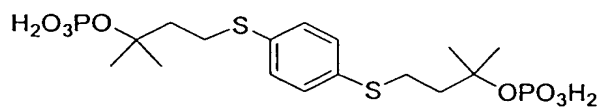


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I-17

2-Methyl-4-[4-(3-methyl-3-sulfo-butylsulfanyl)-phenylsulfanyl]-butane-2-sulfonic acid

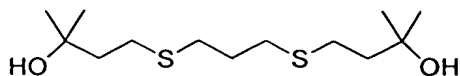
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I-18

Phosphoric acid mono-{1,1-dimethyl-3-[4-(3-methyl-3-phosphonooxy-butylsulfanyl)-
phenylsulfanyl]-propyl} ester

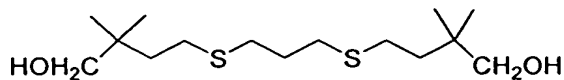
35



Ib-1

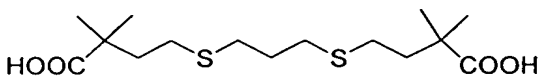
4-[3-(3-Hydroxy-3-methyl-butylsulfanyl)-propylsulfanyl]-2-methyl-butan-2-ol

5



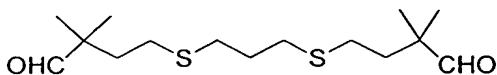
Ib-2

10 4-[3-(4-Hydroxy-3,3-dimethyl-butylsulfanyl)-propylsulfanyl]-2,2-dimethyl-butan-1-ol



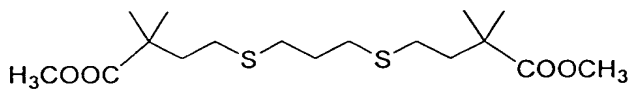
Ib-3

15 4-[3-(3-Carboxy-3-methyl-butylsulfanyl)-propylsulfanyl]-2,2-dimethyl-butyric acid



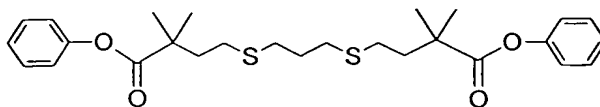
Ib-4

20 4-[3-(3,3-Dimethyl-4-oxo-butylsulfanyl)-propylsulfanyl]-2,2-dimethyl-butyraldehyde



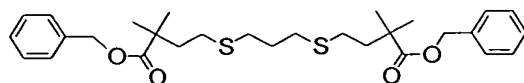
Ib-5

25 4-[3-(3-Methoxycarbonyl-3-methyl-butylsulfanyl)-propylsulfanyl]-2,2-dimethyl-butyric acid
methyl ester



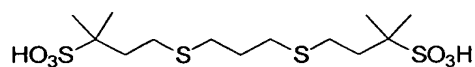
Ib-6

30 2,2-Dimethyl-4-[3-(3-methyl-3-phenoxy-carbonyl-butylsulfanyl)-propylsulfanyl]-butyric
35 acid phenyl ester



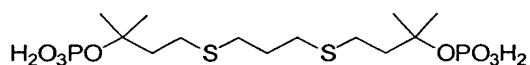
Ib-7

4-[3-(3-Benzoyloxycarbonyl-3-methyl-butylsulfanyl)-propylsulfanyl]-2,2-dimethyl-butylric
acid benzyl ester



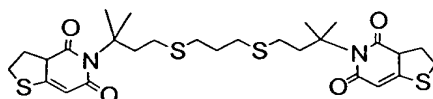
Ib-8

2-Methyl-4-[3-(3-methyl-3-sulfo-butylsulfanyl)-propylsulfanyl]-butane-2-sulfonic acid



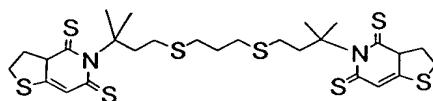
Ib-9

Phosphoric acid
mono-{1,1-dimethyl-3-[3-(3-methyl-3-phosphonooxy-butylsulfanyl)-propylsulfanyl]-propyl
} ester



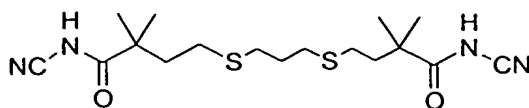
Ib-10

2,12-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-5,9-thi
a-tridecane



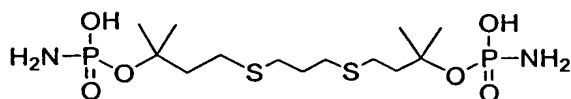
Ib-11

2,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,12-dimethyl-5,9-
thia-tridecane



Ib-12

5 4-[3-(3-Cyanocarbamoyl-3-methyl-butane-1-sulfanyl)-propane-1-sulfanyl]-2,2-dimethyl-but
yrcyanimide

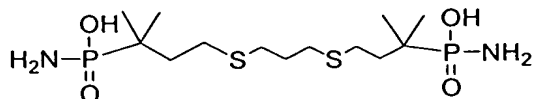


10

Ib-13

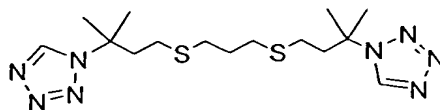
Phosphoramidic acid mono-(3-{3-[3-(amino-hydroxy-phosphoryloxy)-3-methyl-
butylsulfanyl]-propylsulfanyl}-1,1-dimethyl-propyl) ester

15



Ib-14

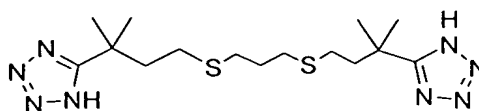
20 3-(Amino-hydroxy-phosphoryloxy)-3-methyl-1-[3-(3-{amino
-hydroxy-phosphoryloxy}-3-methyl-butane-1-sulfanyl)-propane-1-sulfanyl]-butane



25

Ib-15

2,12-Dimethyl-2,12-bis-tetrazol-1-yl-5,9-dithia-tridecane

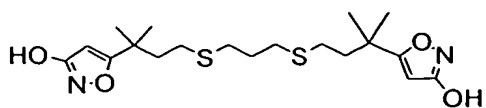


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Ib-16

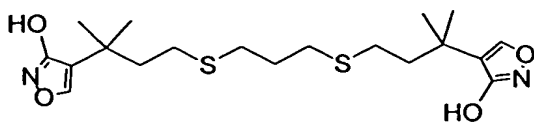
2,12-Dimethyl-2,12-bis-(1H-tetrazol-5-yl)-5,9-dithia-tridecane

35



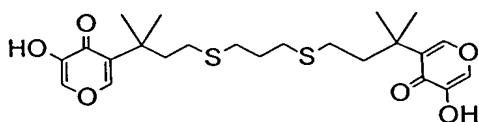
Ib-17

2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-dimethyl-5,9-dithia-tridecane



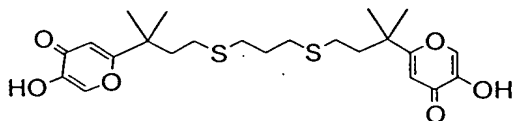
Ib-18

2,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,12-dimethyl-5,9-dithia-tridecane



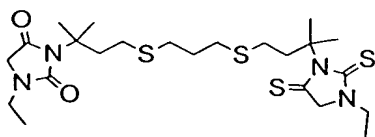
Ib-19

2,12-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,12-dimethyl-5,9-dithia-tridecane



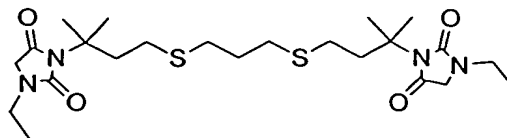
Ib-20

2,12-Bis-(5-hydroxy-4-oxo-4H-pyran-2-yl)-2,12-dimethyl-5,9-dithia-tridecane



Ib-21

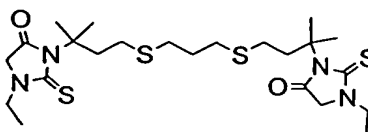
1-Ethyl-3-(3-{3-[3-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3-methyl-butylsulfanyl]-propylsulfanyl}-1,1-dimethyl-propyl)-imidazolidine-2,4-dione



5

Ib-22

2,12-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,12-dimethyl-5,9-dithia-tridecane

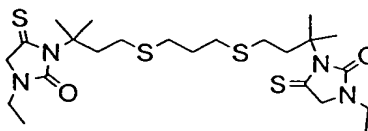


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Ib-23

2,12-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,12-dimethyl-5,9-dithia-tridecane

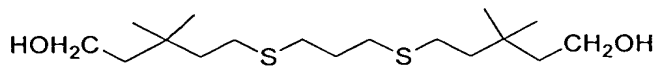
15



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Ib-24

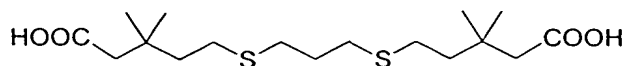
2,12-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,12-dimethyl-5,9-dithia-tridecane



25

Ib-25

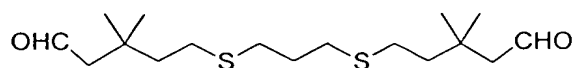
5-[3-(5-Hydroxy-3,3-dimethyl-pentylsulfanyl)-propylsulfanyl]-3,3-dimethyl-pentan-1-ol



30

Ib-26

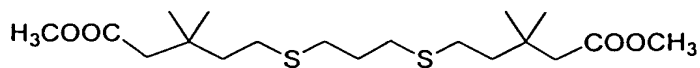
5-[3-(4-Carboxy-3,3-dimethyl-butylsulfanyl)-propylsulfanyl]-3,3-dimethyl-pentanoic acid



35

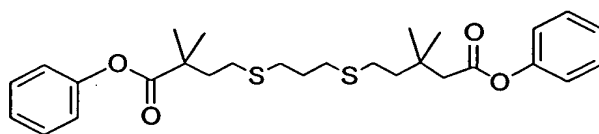
Ib-27

5-[3-(3,3-Dimethyl-5-oxo-pentylsulfanyl)-propylsulfanyl]-3,3-dimethyl-pentanal



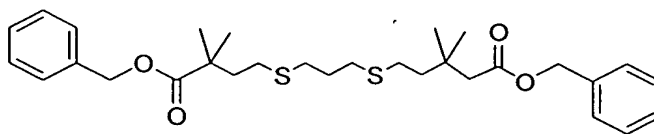
Ib-28

5-[3-(4-Methoxycarbonyl-3,3-dimethyl-butylsulfanyl)-propylsulfanyl]-3,3-dimethyl-pentanoic acid methyl ester



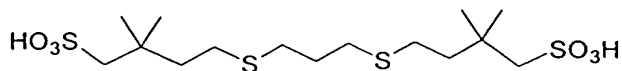
Ib-29

3,3-Dimethyl-5-[3-(3-methyl-3-phenoxy-carbonyl-butylsulfanyl)-propylsulfanyl]-pentanoic acid phenyl ester



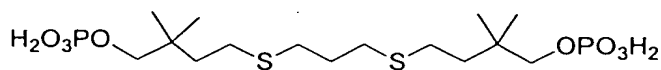
Ib-30

5-[3-(3-Benzoyloxycarbonyl-3-methyl-butylsulfanyl)-propylsulfanyl]-3,3-dimethyl-pentanoic acid benzyl ester



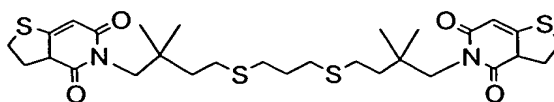
Ib-31

4-[3-(3,3-Dimethyl-4-sulfo-butylsulfanyl)-propylsulfanyl]-2,2-dimethyl-butane-1-sulfonic acid



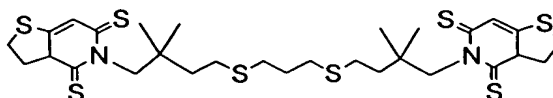
Ib-32

Phosphoric acid mono-{4-[3-(3,3-dimethyl-4-phosphonooxy-butylsulfanyl)-propylsulfanyl]-2,2-dimethyl-butyl} ester



Ib-33

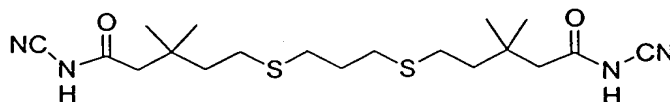
5 1,13-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane



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Ib-34

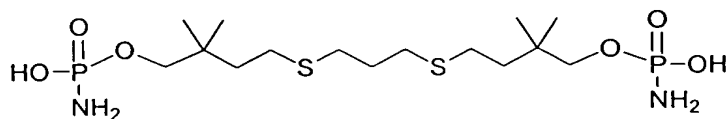
1,13-Bis-(4,6-dithio-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane



15

Ib-35

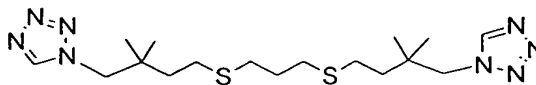
20 5-[3-(4-Cyanocarbamoyl-3,3-dimethyl-butane-1-sulfanyl)-propane-1-sulfanyl]-3,3-dimethyl-pentanoic acid cyanamide



25

Ib-36

Phosphoramidic acid mono-(4-{3-[4-(amino-hydroxy-phosphoryloxy)-3,3-dimethyl-butylsulfanyl]-propylsulfanyl}-2,2-dimethyl-butyl) ester

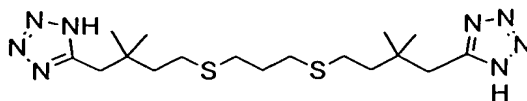


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Ib-37

2,2,12,12-Tetramethyl-1,13-bis-tetrazol-1-yl-5,9-dithia-tridecane

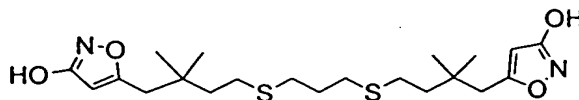
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Ib-38

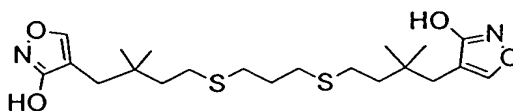
2,2,12,12-Tetramethyl-1,13-bis-(1H-tetrazol-5-yl)-5,9-dithia-tridecane



10

Ib-39

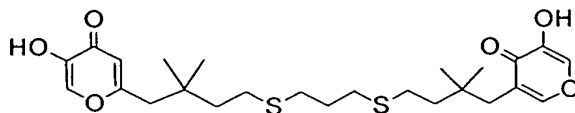
1,13-Bis-(3-hydroxy-isoxazol-5-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane



15

Ib-40

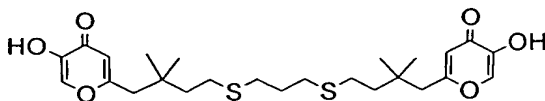
1,13-Bis-(3-hydroxy-isoxazol-4-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane



20

Ib-41

1-(5-Hydroxy-4-oxo-4H-pyran-3-yl)-13-(5-hydroxy-4-oxo-4H-pyran-2-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane

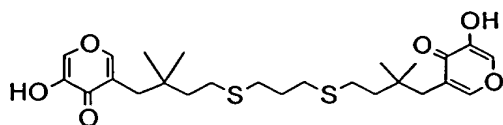


30

Ib-42

1,13-Bis-(5-hydroxy-4-oxo-4H-pyran-2-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane

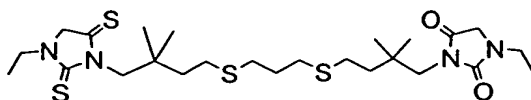
35



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Ib-43

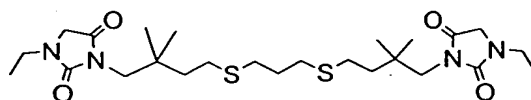
1,13-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane



10

Ib-44

1-Ethyl-3-(4-{3-[4-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3-dimethyl-butylsulfanyl]-propylsulfanyl}-2,2-dimethyl-butyl)-imidazolidine-2,4-dione

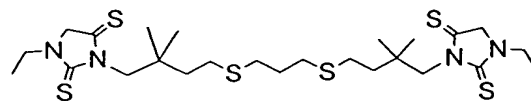


15

Ib-45

1,13-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane

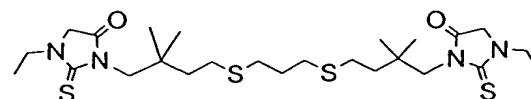
20



25

Ib-46

1,13-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane

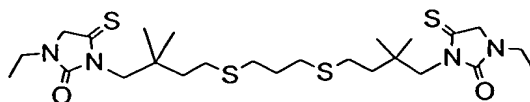


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Ib-47

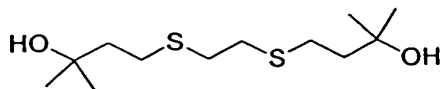
1,13-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane

35



Ib-48

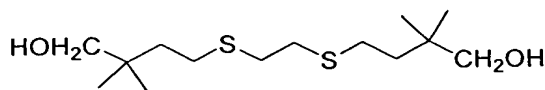
5 1,13-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-5,9-dithia-2,2,12,12-tetramethyl-tridecane



10

Ib-49

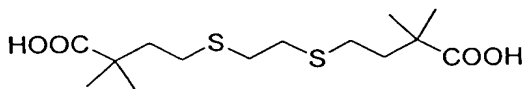
4-[2-(3-Hydroxy-3-methyl-butylsulfanyl)-ethylsulfanyl]-2-methyl-butan-2-ol



15

Ib-50

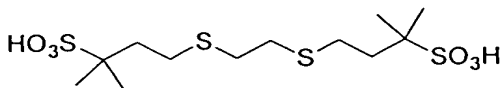
4-[2-(4-Hydroxy-3,3-dimethyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butan-1-ol



20

Ib-51

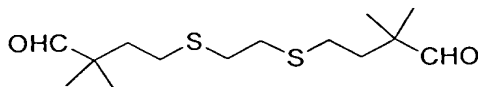
4-[2-(3-Carboxy-3-methyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butyric acid



25

Ib-52

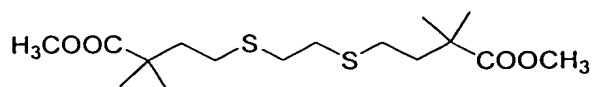
2-Methyl-4-[2-(3-methyl-3-sulfo-butylsulfanyl)-ethylsulfanyl]-butane-2-sulfonic acid



30

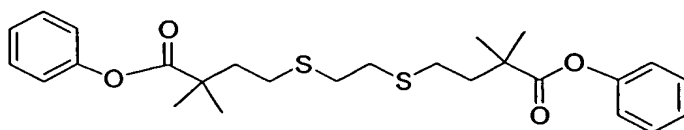
Ib-53

35 4-[2-(3,3-Dimethyl-4-oxo-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butyraldehyde



Ib-54

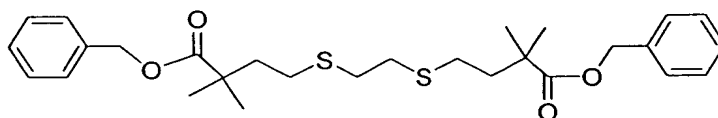
- 5 4-[2-(3-Methoxycarbonyl-3-methyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butylric acid methyl ester



10

Ib-55

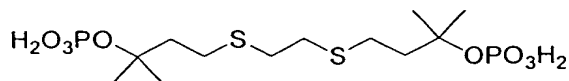
- 2,2-Dimethyl-4-[2-(3-methyl-3-phenoxycarbonyl-butylsulfanyl)-ethylsulfanyl]-butylric acid phenyl ester



15

Ib-56

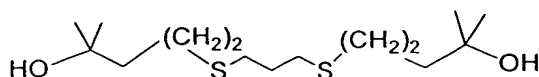
- 20 4-[2-(3-Benzyloxycarbonyl-3-methyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butylric acid benzyl ester



25

Ib-57

- Phosphoric acid mono-{1,1-dimethyl-3-[2-(3-methyl-3-phosphonooxy-butylsulfanyl)-ethylsulfanyl]-propyl} ester

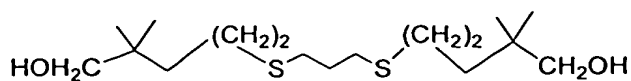


30

Ib-58

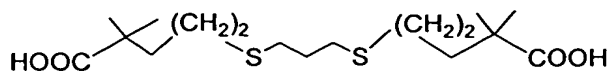
- 5-[3-(4-Hydroxy-4-methyl-pentylsulfanyl)-propylsulfanyl]-2-methyl-pentan-2-ol

35



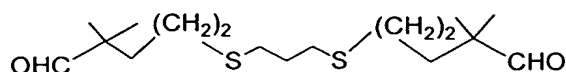
Ib-59

5- $\{3-(5\text{-Hydroxy-4,4-dimethyl-pentylsulfanyl})\text{-propylsulfanyl}\}$ -2,2-dimethyl-pentan-1-ol



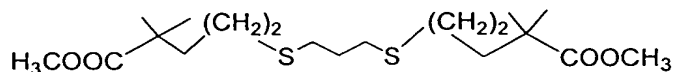
Ib-60

5- $\{3-(4\text{-Carboxy-4-methyl-pentylsulfanyl})\text{-propylsulfanyl}\}$ -2,2-dimethyl-pentanoic acid



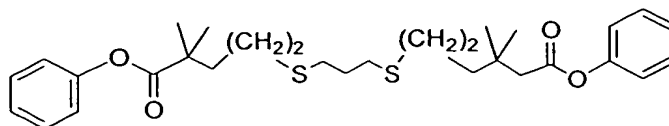
Ib-61

5- $\{3-(4,4\text{-Dimethyl-5-oxo-pentylsulfanyl})\text{-propylsulfanyl}\}$ -2,2-dimethyl-pentanal



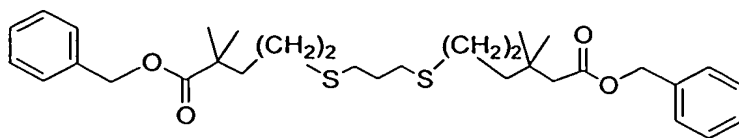
Ib-62

5- $\{3-(4\text{-Methoxycarbonyl-4-methyl-pentylsulfanyl})\text{-propylsulfanyl}\}$ -2,2-dimethyl-pentanoic acid methyl ester



Ib-63

3,3-Dimethyl-6- $\{3-(4\text{-methyl-4-phenoxy-carbonyl-pentylsulfanyl})\text{-propylsulfanyl}\}$ -hexanoic acid phenyl ester

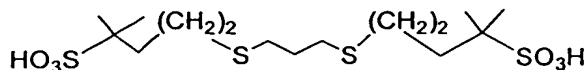


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Ib-64

6-[3-(4-Benzoyloxycarbonyl-4-methyl-pentylsulfanyl)-propylsulfanyl]-3,3-dimethyl-hexanoic acid benzyl ester

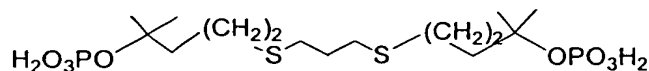
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Ib-65

2-Methyl-5-[3-(4-methyl-4-sulfo-pentylsulfanyl)-propylsulfanyl]-pentane-2-sulfonic acid

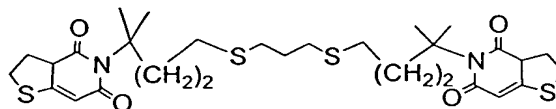
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Ib-66

Phosphoric acid mono-{1,1-dimethyl-4-[3-(4-methyl-4-phosphonooxy-pentylsulfanyl)-propylsulfanyl]-butyl} ester

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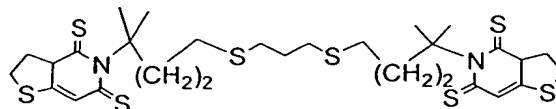


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Ib-67

2,14-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-6,10-dithia-2,14-dimethyl-pentadecane

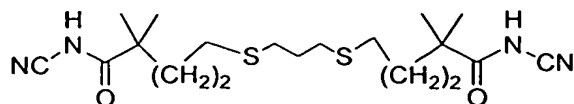
30



Ib-68

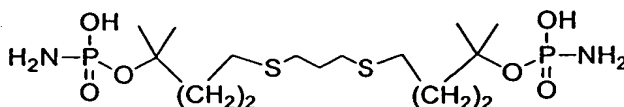
2,14-Bis-(4,6-dithio-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-6,10-dithia-2,14-dimethyl-pentadecane

35



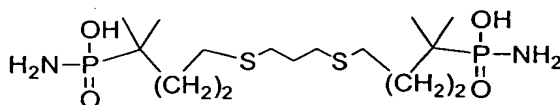
Ib-69

5-[3-(4-Cyanocarbamoyl-4-methyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-2,2-dimethyl-pentanoic acid cyanamide



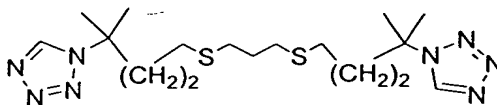
Ib-70

Phosphoramidic acid mono-(4-{3-[4-(amino-hydroxy-phosphoryloxy)-4-methyl-pentylsulfanyl]-propylsulfanyl}-1,1-dimethyl-butyl) ester



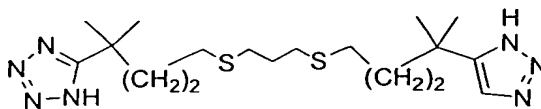
Ib-71

4-(Amino-hydroxy-phosphoryloxy)-4-methyl-1-[3-(4-{amino-hydroxy-phosphoryloxy}-4-methyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-pentane



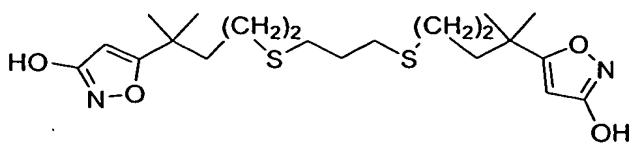
Ib-72

1-(1,1-Dimethyl-4-{3-[4-methyl-4-(1H-[1,2,3]triazol-4-yl)-pentylsulfanyl]-propylsulfanyl}-butyl)-1H-tetrazole



Ib-73

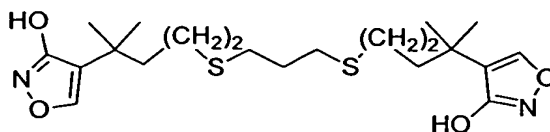
5-(1,1-Dimethyl-4-{3-[4-methyl-4-(3H-[1,2,3]triazol-4-yl)-pentylsulfanyl]-propylsulfanyl}-butyl)-1H-tetrazole



5

Ib-74

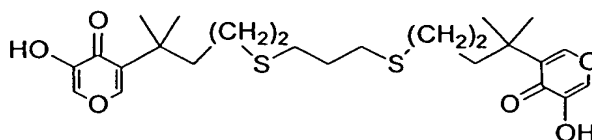
2,14-Bis-(3-hydroxy-isoxazol-5-yl)-2,14-dimethyl-6,10-dithia-pentadecane



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Ib-75

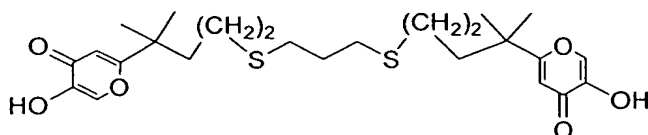
2,14-Bis-(3-hydroxy-isoxazol-4-yl)-2,14-dimethyl-6,10-dithia-pentadecane



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Ib-76

2,14-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-2,14-dimethyl-6,10-dithia-pentadecane

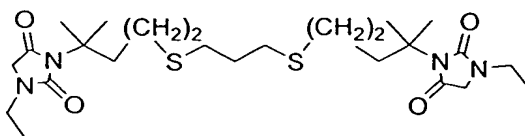


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Ib-77

2-(5-Hydroxy-4-oxo-4H-pyran-2-yl)-2,14-dimethyl-6,10-dithia-14-(5-methyl-4-oxo-4H-pyran-2-yl)-pentadecane

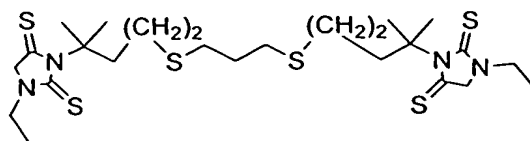
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Ib-78

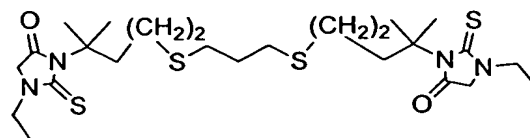
2,14-Bis-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,14-dimethyl-6,10-dithia-pentadecane



5

Ib-79

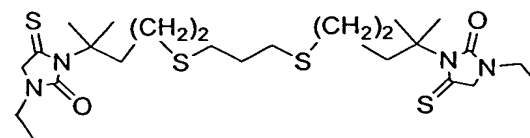
2,14-Bis-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-2,14-dimethyl-6,10-dithia-pentadecane



10

Ib-80

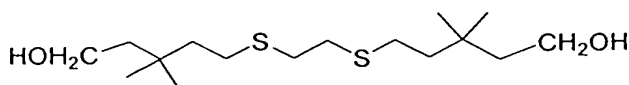
2,14-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-2,14-dimethyl-6,10-dithia-pentadecane



15

Ib-81

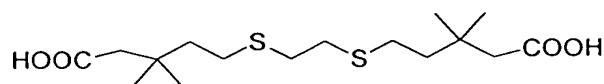
2,14-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-2,14-dimethyl-6,10-dithia-pentadecane



25

Ib-82

5-[2-(5-Hydroxy-3,3-dimethyl-pentylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentan-1-ol

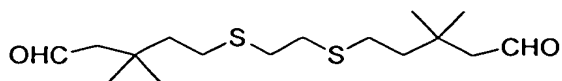


30

Ib-83

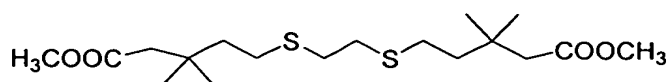
5-[2-(4-Carboxy-3,3-dimethyl-butylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentanoic acid

35



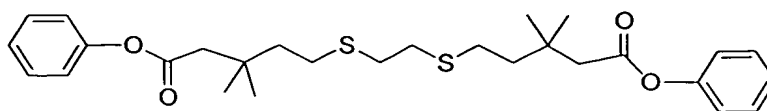
Ib-84

5- [2-(3,3-Dimethyl-5-oxo-pentylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentanal



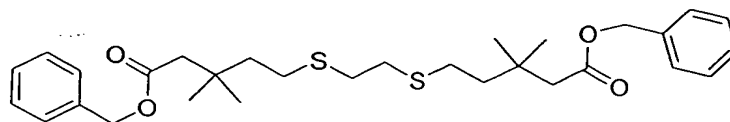
Ib-85

5- [2-(4-Methoxycarbonyl-3,3-dimethyl-butylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentanoic acid methyl ester



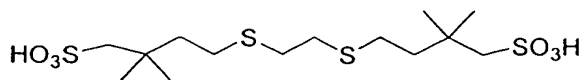
Ib-86

5- [2-(3,3-Dimethyl-4-phenoxy-carbonyl-butylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentanoic acid phenyl ester



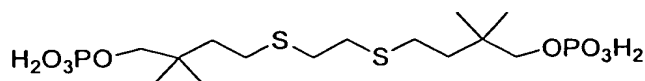
Ib-87

5- [2-(4-Benzylloxycarbonyl-3,3-dimethyl-butylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentanoic acid benzyl ester



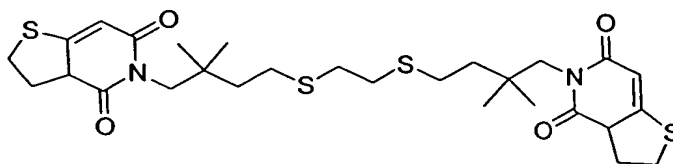
Ib-88

4- [2-(3,3-Dimethyl-4-sulfo-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butane-1-sulfonic acid



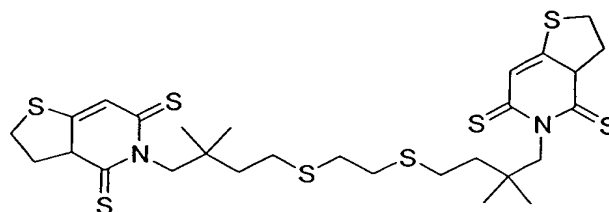
Ib-89

Phosphoric acid mono-{4-[2-(3,3-dimethyl-4-phosphonooxy-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butyl} ester



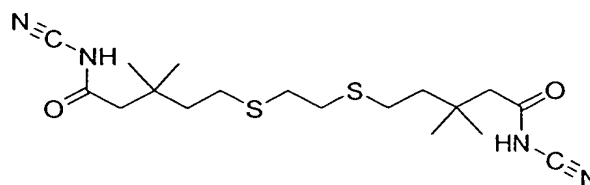
Ib-90

1,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-5,8-dithio-2,2,11,11-tetramethyl-dodecane



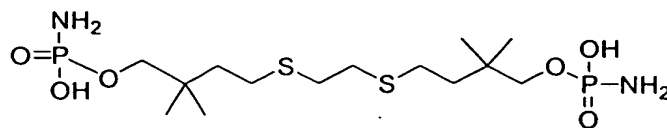
Ib-91

1,12-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-5,8-dithio-2,2,11,11-tetramethyl-dodecane



Ib-92

5-[2-(4-Cyanocarbamoyl-3,3-dimethyl-butane-1-sulfanyl)-ethanesulfanyl]-3,3-dimethyl-pentanoic acid cyanamide

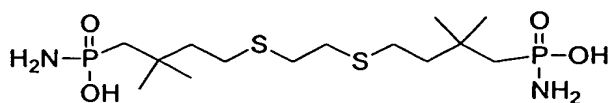


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Ib-93

Phosphoramidic acid mono-(4-{2-[4-(amino-hydroxy-phosphoryloxy)-3,3-dimethyl-butylsulfanyl]-ethylsulfanyl}-2,2-dimethyl-butyl) ester

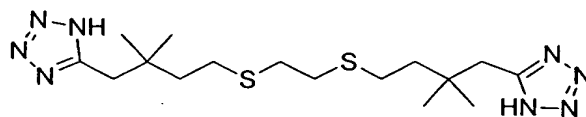
10



Ib-94

1-[2-(3,3-Dimethyl-4 {amino-hydroxy-phosphoryloxy}-butane-1-sulfanyl)-ethanesulfanyl]-3,3-dimethyl-4 {amino-hydroxy-phosphoryloxy}-butane

15

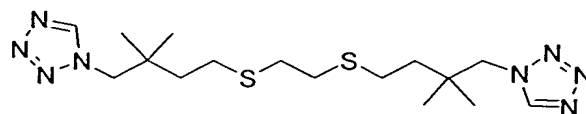


20

Ib-95

2,2,11,11-Tetramethyl-1,12-bis-(1H-tetrazol-5-yl)-5,8-dithio-dodecane

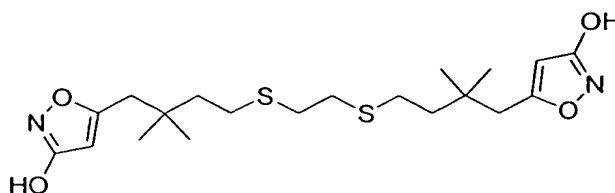
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Ib-96

2,2,11,11-Tetramethyl-1,12-bis-(tetrazol-1-yl)-5,8-dithio-dodecane

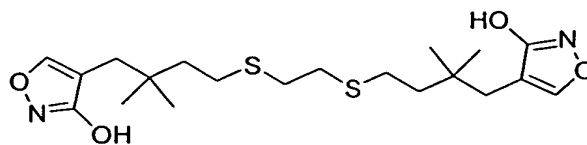
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Ib-97

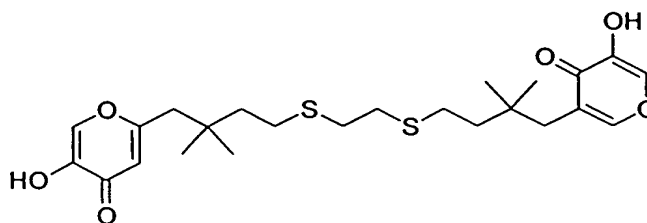
1,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,2,11,11-tetramethyl-5,8-dithio-dodecane



5

Ib-98

1,12-Bis-(3-hydroxy-isoxazol-4-yl)-2,2,11,11-tetramethyl-5,8-dithio-dodecane



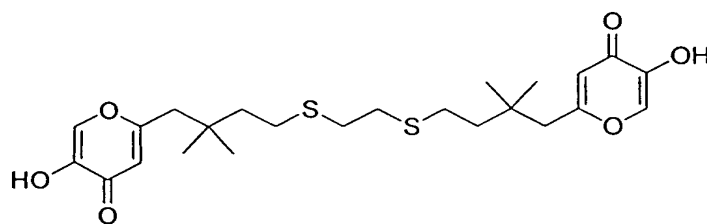
10

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Ib-99

1-(5-Hydroxy-4-oxo-4H-pyran-3-yl)-12-(5-hydroxy-4-oxo-4H-pyran-2-yl)-5,8-dithio-2,2,11,11-tetramethyl-dodecane

20



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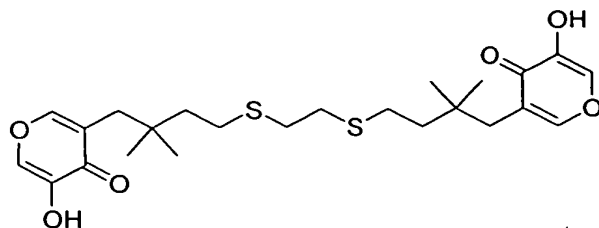
Ib-100

1,12-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-5,8-dithio-2,2,11,11-tetramethyl-dodecane

30

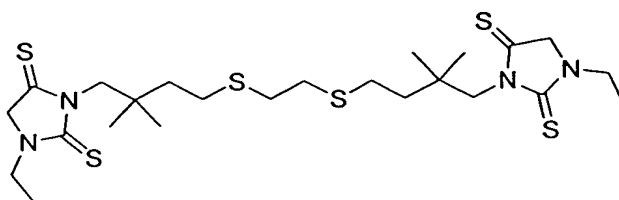
35

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**Ib-101**

1,12-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-5,8-dithio-2,2,11,11-tetramethyl-dodecane

10

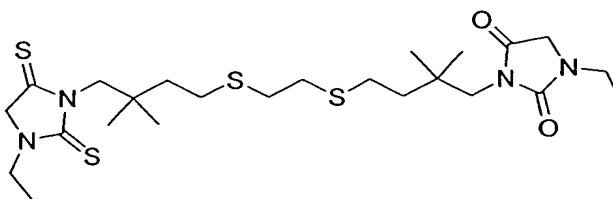


15

Ib-102

1-Ethyl-3-(4-{2-[4-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3-dimethyl-butylsulfanyl]-ethylsulfanyl}-2,2-dimethyl-butyl)-imidazolidine-2,4-dithione

20



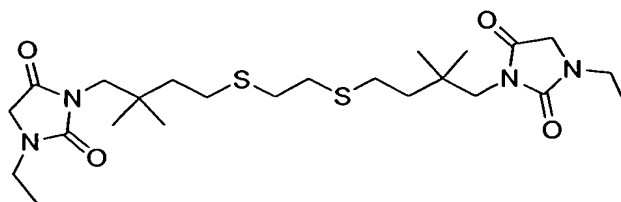
25

Ib-103

1-Ethyl-3-(4-{2-[4-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3-dimethyl-butylsulfanyl]-ethylsulfanyl}-2,2-dimethyl-butyl)-imidazolidine-2,4-dione

30

35

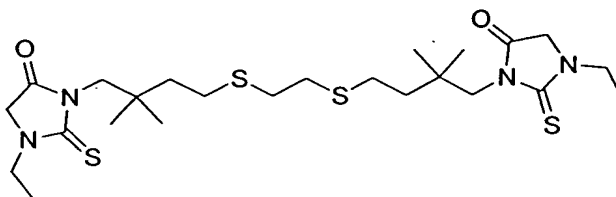


5

Ib-104

1-Ethyl-3-[12-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-2,2,11,11-tetramethyl-5,8-dithio-dodecyl]-imidazolidine-2,4-dione

10

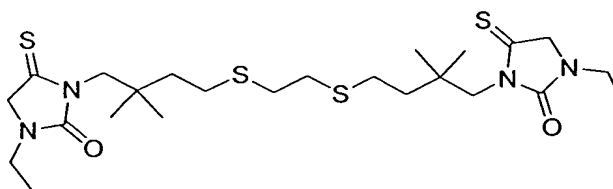


15

Ib-105

1,12-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-5,8-dithio-2,2,11,11-tetramethyl-dodecane

20

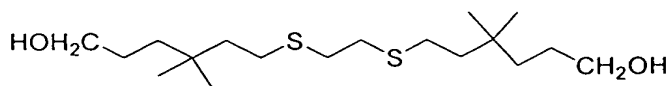


25

Ib-106

1,12-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-5,8-dithio-2,2,11,11-tetramethyl-dodecane

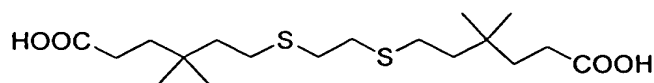
30



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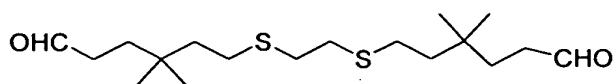
Ib-107

6-[2-(6-Hydroxy-3,3-dimethyl-hexylsulfanyl)-ethylsulfanyl]-4,4-dimethyl-hexan-1-ol



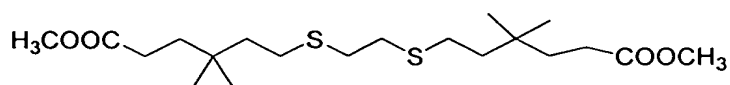
Ib-108

5 6-[2-(5-Carboxy-3,3-dimethyl-pentylsulfanyl)-ethylsulfanyl]-4,4-dimethyl-hexanoic acid



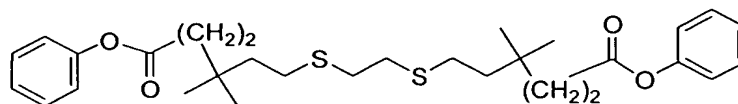
Ib-109

10 6-[2-(3,3-Dimethyl-6-oxo-hexylsulfanyl)-ethylsulfanyl]-4,4-dimethyl-hexanal



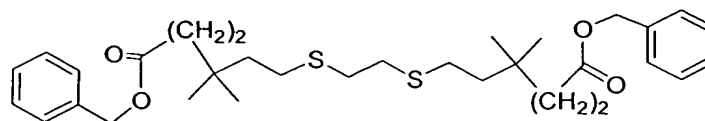
Ib-110

15 6-[2-(5-Methoxycarbonyl-3,3-dimethyl-pentylsulfanyl)-ethylsulfanyl]-4,4-dimethyl-hexanoic acid methyl ester



Ib-111

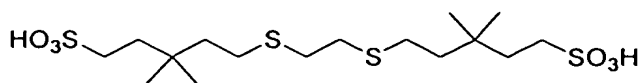
20 6-[2-(3,3-Dimethyl-5-phenoxy-carbonyl-pentylsulfanyl)-ethylsulfanyl]-4,4-dimethyl-hexanoic acid phenyl ester



Ib-112

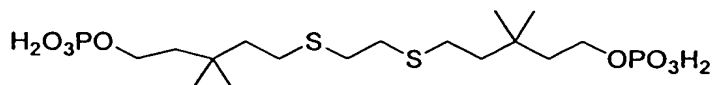
30 6-[2-(5-Benzyloxycarbonyl-3,3-dimethyl-pentylsulfanyl)-ethylsulfanyl]-4,4-dimethyl-hexanoic acid benzyl ester

35



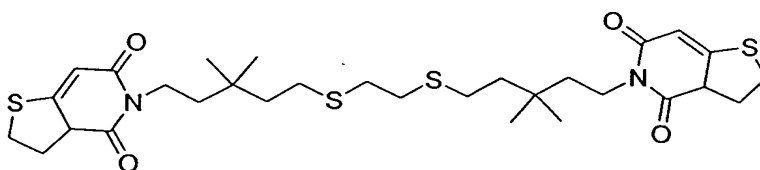
Ib-113

5 5-[2-(3,3-Dimethyl-5-sulfo-pentylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentane-1-sulfonic acid



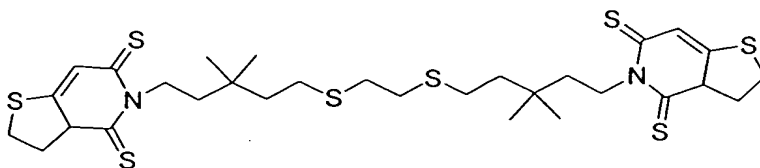
Ib-114

10 Phosphoric acid mono- {5-[2-(3,3-dimethyl-5-phosphonooxy-pentylsulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentyl} ester



Ib-115

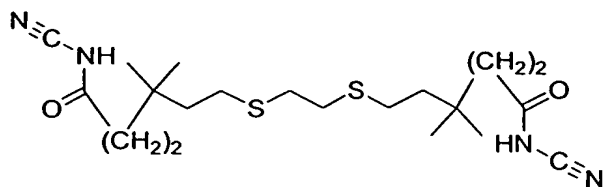
20 1,14-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane



Ib-116

30 1,14-Bis-(4,6-dithio-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane

35

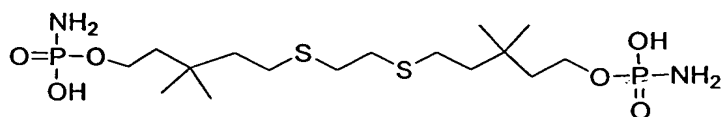


5

Ib-117

6-[2-(5-Cyanocarbamoyl-3,3-dimethyl-pentane-1-sulfanyl)-ethanesulfanyl]-4,4-dimethyl-hexanoic acid cyanimide

10

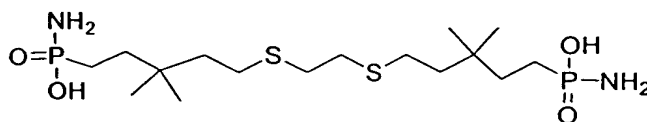


15

Ib-118

Phosphoramidic acid mono-(5-{2-[5-(amino-hydroxy-phosphoryloxy)-3,3-dimethyl-pentylsulfanyl]-ethylsulfanyl}-3,3-dimethyl-pentyl) ester

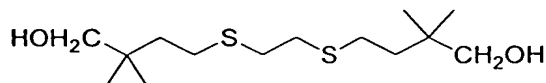
20



25

Ib-119

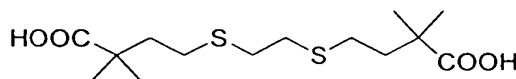
1-[2-(3,3-Dimethyl-5-{amino-hydroxy-phosphoryloxy}-pentane-1-sulfanyl)-ethanesulfanyl]-3,3-dimethyl-5-{amino-hydroxy-phosphoryloxy}



30

Ib-120

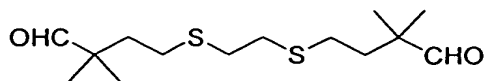
4-[2-(4-Hydroxy-3,3-dimethyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butan-1-ol



35

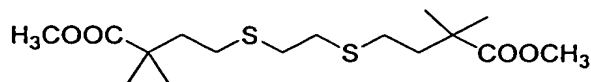
Ib-121

4-[2-(3-Carboxy-3-methyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butyric acid



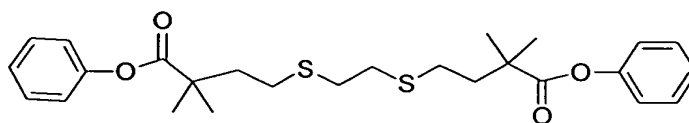
Ib-122

5 4-[2-(3,3-Dimethyl-4-oxo-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butylaldehyde



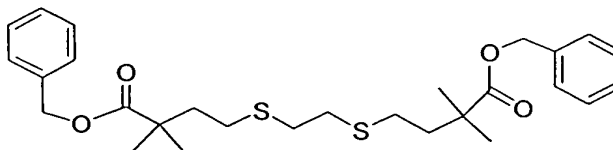
Ib-123

10 4-[2-(3-Methoxycarbonyl-3-methyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butyl methyl ester



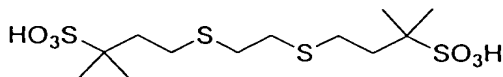
Ib-124

20 2,2-Dimethyl-4-[2-(3-methyl-3-phenoxy-carbonyl-butylsulfanyl)-ethylsulfanyl]-butyric acid phenyl ester



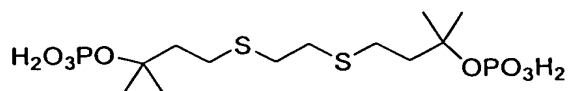
Ib-125

30 4-[2-(3-Benzoyloxycarbonyl-3-methyl-butylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-butyl benzyloxy ester



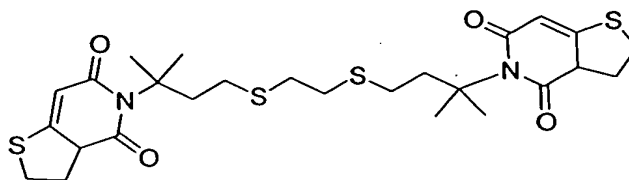
Ib-126

35 2-Methyl-4-[2-(3-methyl-3-sulfo-butylsulfanyl)-ethylsulfanyl]-butane-2-sulfonic acid



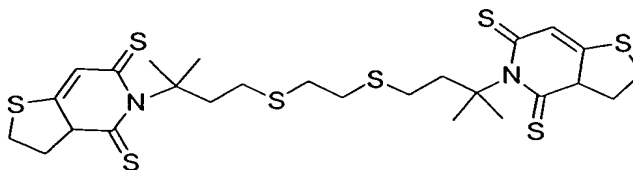
Ib-127

5 Phosphoric acid mono-{1,1-dimethyl-3-[2-(3-methyl-3-phosphonooxy-butylsulfanyl)-
ethylsulfanyl]-propyl} ester



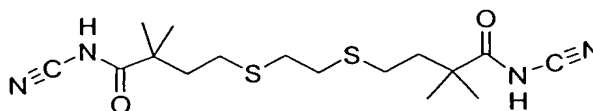
Ib-128

15 2,11-Bis-(4,6-dioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-5,8-
dithio-dodecane



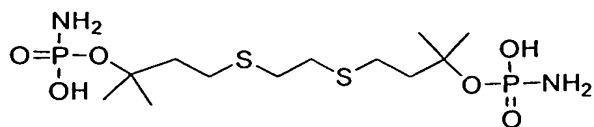
Ib-129

25 2,11-Bis-(4,6-dithioxo-2,3,3a,6-tetrahydro-4H-thieno[3,2-c]pyridin-5-yl)-2,11-dimethyl-
5,8-dithio-dodecane



Ib-130

35 4-[2-(3-Cyanocarbamoyl-3-methyl-butane-1-sulfanyl)-ethanesulfanyl]-2,2-dimethyl-butyracy-
animide

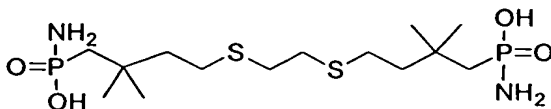


5

Ib-131

Phosphoramidic acid mono-(3-{2-[3-(amino-hydroxy-phosphoryloxy)-3-methyl-butylsulfanyl]-ethylsulfanyl}-1,1-dimethyl-propyl) ester

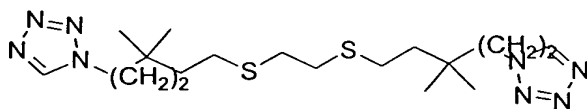
10



Ib-132

15

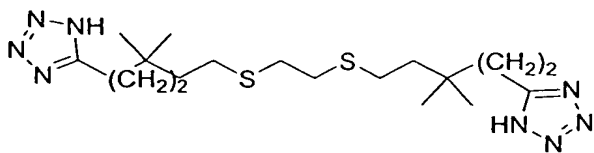
1-{5-[2-(3,3-Dimethyl-5-{tetrazol-1-yl}-pentane-1-sulfanyl)-ethylsulfanyl]-3,3-dimethyl-pentyl}-1*H*-tetrazole



20

Ib-133

6,9-Dithio-3,3,12,12-tetramethyl-1,14-bis-tetrazol-1-yl-tetradecane



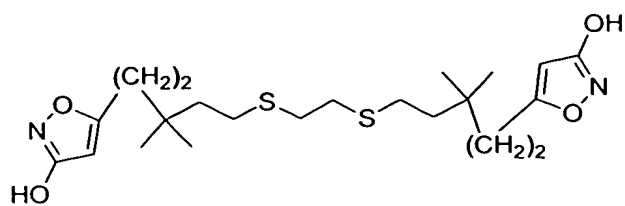
25

Ib-134

30

6,9-Dithio-3,3,12,12-tetramethyl-1,14-bis-(1*H*-tetrazol-5-yl)-tetradecane

35

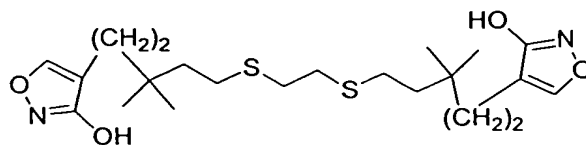


5

Ib-135

1,14-Bis-(3-hydroxy-isoxazol-5-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane

10

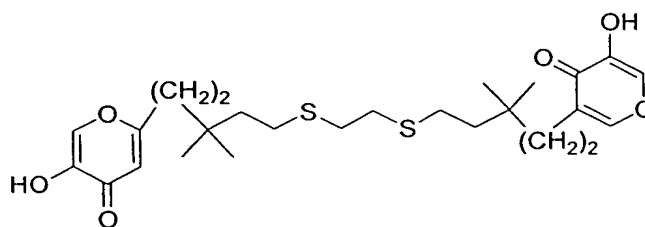


15

Ib-136

1,14-Bis-(3-hydroxy-isoxazol-4-yl)-3,3,12,12-tetramethyl-tetradecane-6,9-dithiol

20



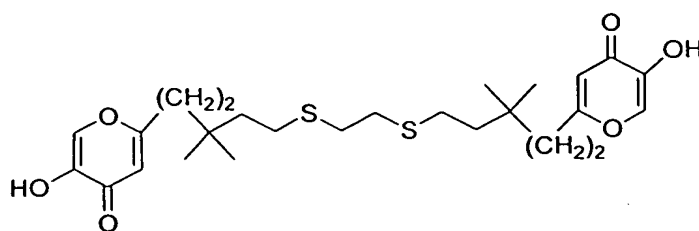
25

Ib-137

1-(5-Hydroxy-4-oxo-4H-pyran-2-yl)-14-(5-hydroxy-4-oxo-4H-pyran-3-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane

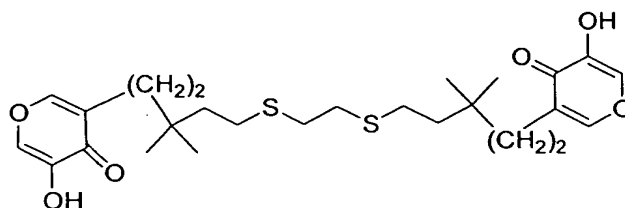
30

35



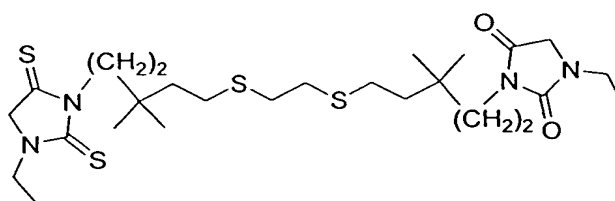
Ib-138

1,14-Bis-(5-hydroxy-4-oxo-4H-pyran-2-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane



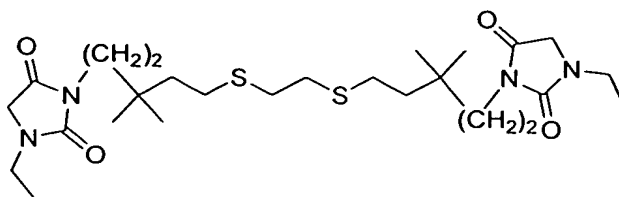
Ib-139

1,14-Bis-(5-hydroxy-4-oxo-4H-pyran-3-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane



Ib-140

1-Ethyl-3-(5-{2-[5-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3-dimethyl-pentylsulfanyl]-ethylsulfanyl}-3,3-dimethyl-pentyl)-imidazolidine-2,4-dione

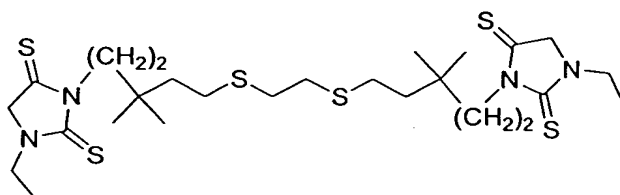


5

Ib-141

1-Ethyl-3-[14-(3-ethyl-2,5-dioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dithio-tetradecyl]-imidazolidine-2,4-dione

10

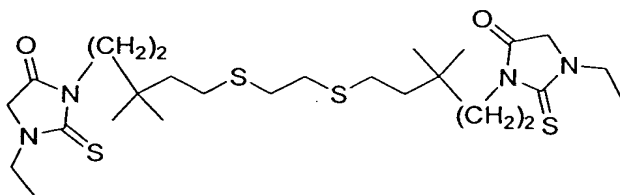


15

Ib-142

1-Ethyl-3-[14-(3-ethyl-2,5-dithioxo-imidazolidin-1-yl)-3,3,12,12-tetramethyl-6,9-dithio-tetradecyl]-imidazolidine-2,4-dithione

20



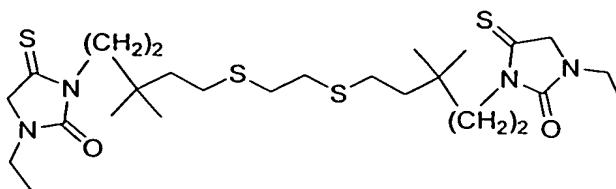
25

Ib-143

1,14-Bis-(3-ethyl-5-oxo-2-thioxo-imidazolidin-1-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane

30

35

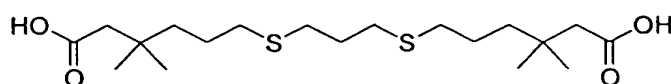


5

Ib-144

1,14-Bis-(3-ethyl-2-oxo-5-thioxo-imidazolidin-1-yl)-6,9-dithio-3,3,12,12-tetramethyl-tetradecane-

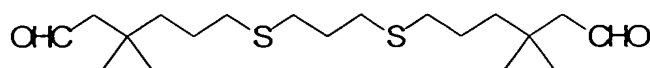
10



Ib-145

6-[3-(5-Carboxy-4,4-dimethyl-pentylsulfanyl)-propylsulfanyl]-3,3-dimethyl-hexanoic acid

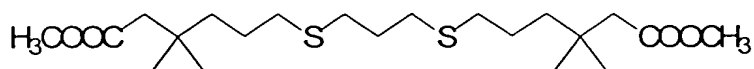
15



Ib-146

6-[3-(4,4-Dimethyl-6-oxo-hexylsulfanyl)-propylsulfanyl]-3,3-dimethyl-hexanal

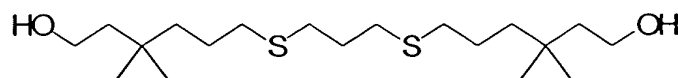
20



Ib-147

6-[3-(5-Methoxycarbonyl-4,4-dimethyl-pentylsulfanyl)-propylsulfanyl]-3,3-dimethyl-hexanoic acid methyl ester

25

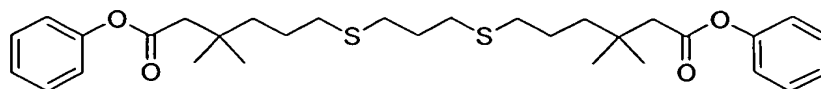


30

Ib-148

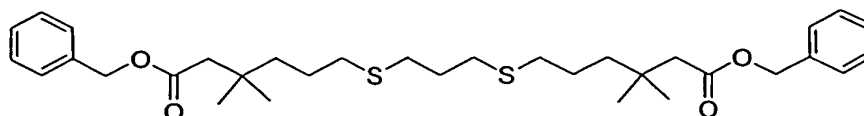
6-[3-(6-Hydroxy-4,4-dimethyl-hexylsulfanyl)-propylsulfanyl]-3,3-dimethyl-hexan-1-ol

35



Ib-149

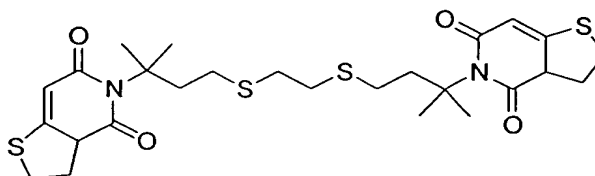
5 6-[3-(4,4-Dimethyl-5-phenoxy-carbonyl-pentylsulfanyl)-propylsulfanyl]-3,3-dimethyl-hexanoic acid phenyl ester



10

Ib-150

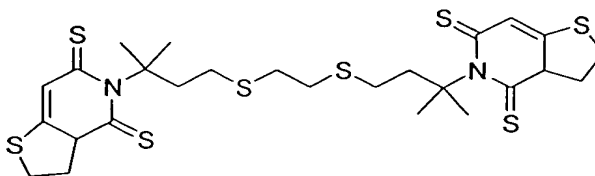
15 6-[3-(5-Benzyloxycarbonyl-4,4-dimethyl-pentylsulfanyl)-propylsulfanyl]-3,3-dimethyl-hexanoic acid benzyl ester



20

Ib-151

5-(3-{2-[3-(3-Ethyl-2,6-dioxo-3,6-dihydro-2H-pyridin-1-yl)-3-methyl-butane-1-sulfanyl]-ethanesulfanyl}-1,1-dimethyl-propyl)-3,3a-dihydro-2H-thieno[3,2-c]pyridine-4,6-dione



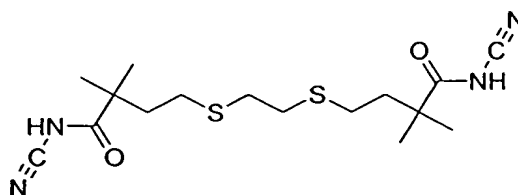
25

Ib-152

30 3-(3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dithione)-3-methyl-1-[2-(3-{3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dithione}-3-methyl-butane-1-sulfanyl)-ethanesulfanyl]-butane

35

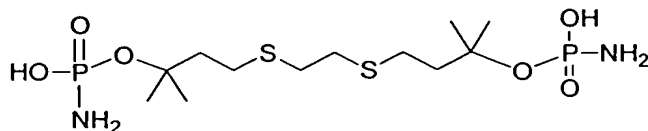
5



Ib-153

4-[2-(3-Cyanocarbamoyl-3-methyl-butane-1-sulfanyl)-ethanesulfinyl]-2,2-dimethyl-cyanobutyramide

10

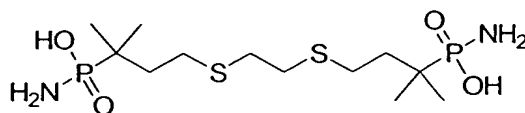


15

Ib-154

Phosphoramidic acid mono-(3-{2-[3-(amino-hydroxy-phosphoryloxy)-3-methyl-butylsulfanyl]-ethylsulfanyl}-1,1-dimethyl-propyl) ester

20

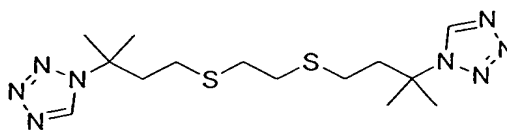


25

Ib-155

3-Methyl-3-tetrazol-1-yl-1-[2-(3-methyl-3-tetrazol-1-yl-butane-1-sulfanyl)-ethanesulfinyl]-butane

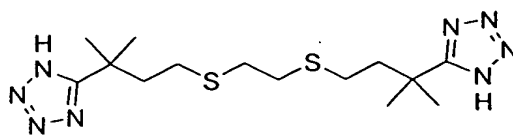
30



Ib-156

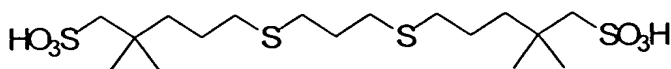
3-Methyl-3-tetrazol-1-yl-1-[2-(3-methyl-3-tetrazol-1-yl-butane-1-sulfanyl)-ethanesulfinyl]-butane

35



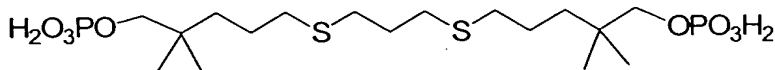
Ib-157

3-Methyl-3-1*H*-tetrazol-5-yl-1-[2-(3-methyl-3-1*H*-
tetrazol-5-yl-butane-1-sulfanyl)-ethanesulfanyl]-butane



Ib-158

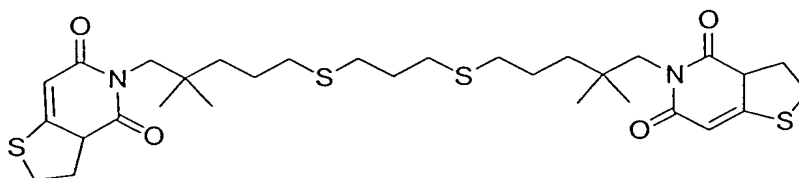
5-[3-(4,4-Dimethyl-5-sulfo-pentylsulfanyl)-propylsulfanyl]-2,2-dimethyl-pentane-1-sulfonic
acid



Ib-159

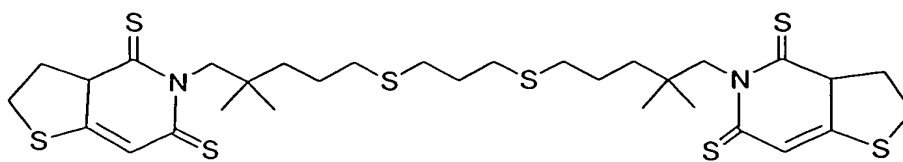
Phosphoric acid

mono-{5-[3-(4,4-dimethyl-5-phosphonooxy-pentylsulfanyl)-propylsulfanyl]-2,2-dimethyl
-pentyl} ester



Ib-160

1-[3-(5-{3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dione}-4,4-Dimethyl-pentane-1-
sulfanyl)-propane-1-sulfanyl]-5-(3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dione)-4,4-
dimethyl-pentane

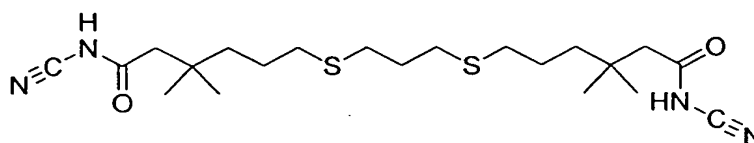


5

Ib-161

1-[3-(5-{3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dithione}-4,4-Dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dithione)-4,4-dimethyl-pentane

10

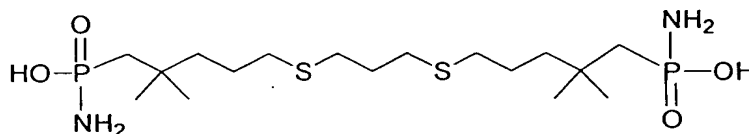


15

Ib-162

6-[3-(5-Cyanocarbamoyl-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-3,3-dimethyl-hexanoic acid cyanamide

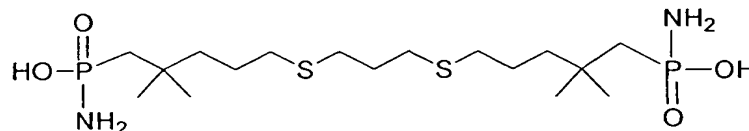
20



Ib-163

Phosphoramidic acid mono-[16-(amino-hydroxy-phosphoryloxy)-4,4,15,15-tetramethyl-7,11-dioxo-hexadecyl] thioester

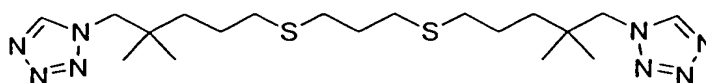
30



Ib-164

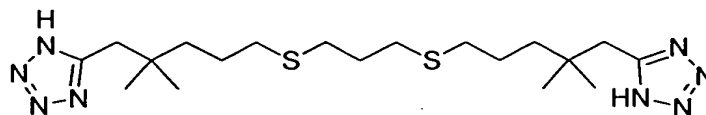
4,4-Dimethyl-5-tetrazol-1-yl-1-[3-(4,4-dimethyl-5-tetrazol-1-yl-pentane-1-sulfanyl)-propane-1-sulfanyl]-pentane

35



Ib-165

5 4,4-Dimethyl-5-tetrazol-1-yl-1-[3-(4,4-dimethyl-5-tetrazol-1-yl-pentane-1-sulfanyl)-propane
-1-sulfanyl]-pentane

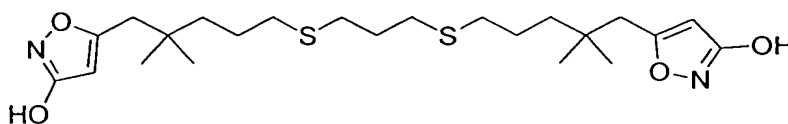


10

Ib-166

4,4-Dimethyl-5-1*H*-tetrazol-5-yl-1-[3-(4,4-dimethyl-5-1*H*-
tetrazol-5-yl-pentane-1-sulfanyl)-propane-1-sulfanyl]-pentane

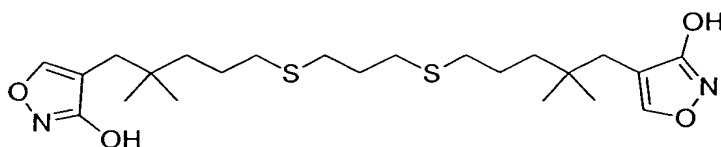
15



20

Ib-167

1-[3-(5-isoxazol-5-yl-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-isoxazol-5-yl
-4,4-dimethyl-hexane

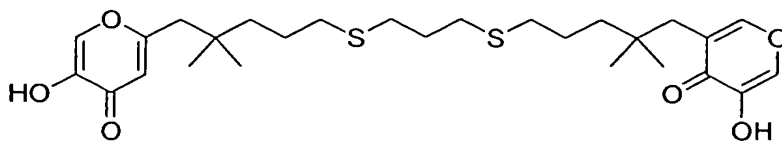


25

Ib-168

30 1-[3-(5-isoxazol-4-yl-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-isoxazol-4-yl
-4,4-dimethyl-hexane

35

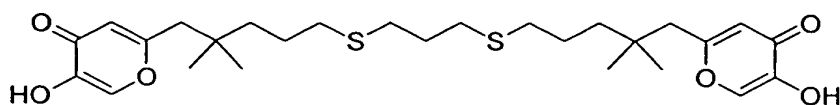


5

Ib-169

1-[3-(5-{5-Hydroxy-4-oxo-4H-pyran-3-yl}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(5-hydroxy-4-oxo-4H-pyran-2-yl)-4,4-dimethyl-pentane

10

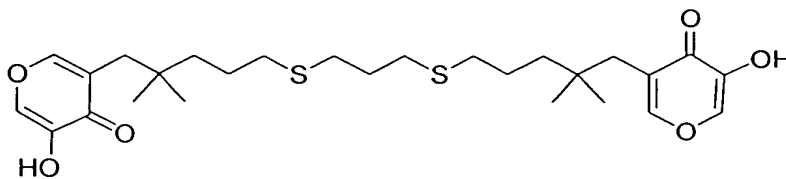


Ib-170

15

1-[3-(5-{5-Hydroxy-4-oxo-4H-pyran-2-yl}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(5-hydroxy-4-oxo-4H-pyran-2-yl)-4,4-dimethyl-pentane

20

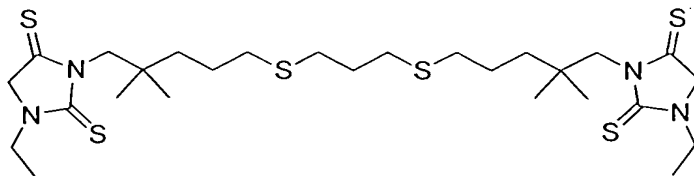


Ib-171

25

1-[3-(5-{5-Hydroxy-4-oxo-4H-pyran-3-yl}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(5-hydroxy-4-oxo-4H-pyran-3-yl)-4,4-dimethyl-pentane

30

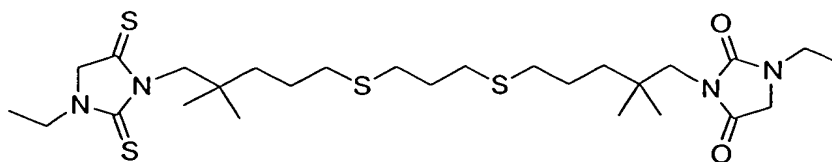


Ib-172

35

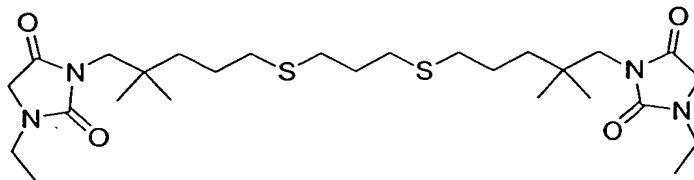
1-[3-(5-{1-ethyl-2,4-dithioxo-imidazolidinyl}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(1-ethyl-2,4-dithioxo-imidazolidinyl)-4,4-dimethyl-pentane

5

**Ib-173**

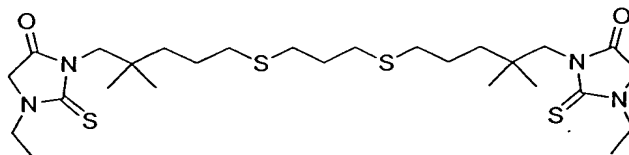
10 1-[3-(5-{1-ethyl-2,4-dithioxo-imidazolidinyl}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(1-ethyl-2,4-dioxo-imidazolidinyl)-4,4-dimethyl-pentane

15

**Ib-174**

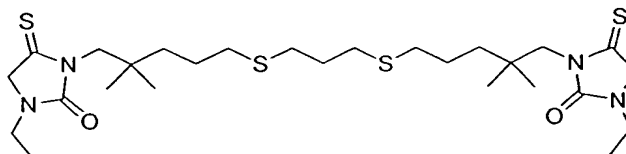
20 1-[3-(5-{1-ethyl-2,4-dioxo-imidazolidinyl}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(1-ethyl-2,4-dioxo-imidazolidinyl)-4,4-dimethyl-pentane

25

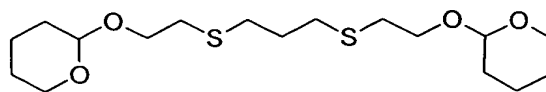
**Ib-175**

1-[3-(5-{1-ethyl-2-thioxo-imidazolidin-4-one}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-4-(1-ethyl-2-thioxo-imidazolidin-4-one)-4,4-dimethyl-pentane

30

**Ib-176**

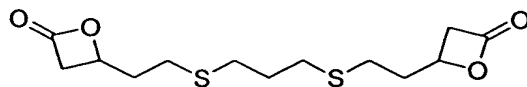
35 1-[3-(5-{1-ethyl-4-thioxo-imidazolidin-2-one}-4,4-dimethyl-pentane-1-sulfanyl)-propane-1-sulfanyl]-5-(1-ethyl-4-thioxo-imidazolidin-2-one)-4,4-dimethyl-pentane



5

Ic-1

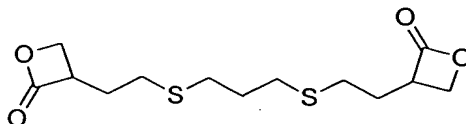
1,9-Bis-(tetrahydro-pyran-2-yloxy)-3,7-dithia-nonane



10

Ic-2

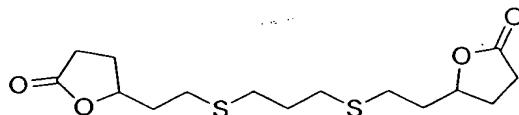
1,9-Bis-(4-oxo-oxetan-2-yl)-3,7-dithia-nonane



15

Ic-3

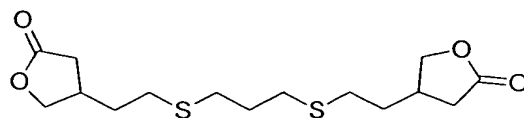
1,9-Bis-(2-oxo-oxetan-3-yl)-3,7-dithia-nonane



20

Ic-4

1,9-Bis-(5-oxo-tetrahydrofuran-2-yl)-3,7-dithia-nonane

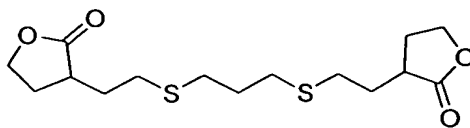


30

Ic-5

1,9-Bis-(5-oxo-tetrahydrofuran-3-yl)-3,7-dithia-nonane

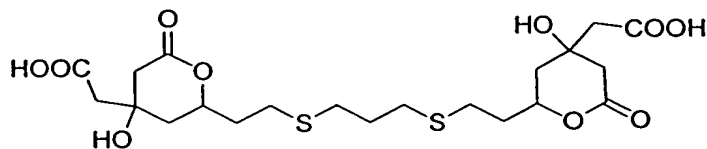
35



5

Ic-6

1,9-Bis-(2-oxo-tetrahydrofuran-3-yl)-3,7-dithia-nonane

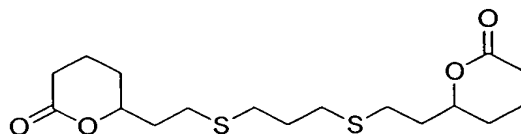


10

Ic-7

[2-(2-{3-[2-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethylsulfanyl]-propylsulfanyl}-ethyl)-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl]-acetic acid

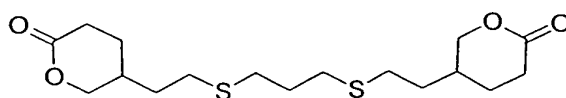
15



20

Ic-8

1,9-Bis-(6-oxo-tetrahydropyran-2-yl)-3,7-dithia-nonane

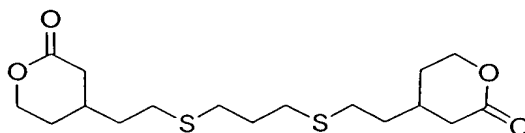


25

Ic-9

1,9-Bis-(6-oxo-tetrahydropyran-3-yl)-3,7-dithia-nonane

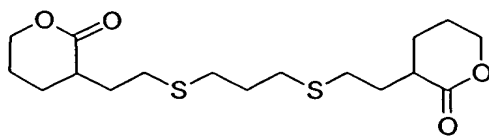
30



35

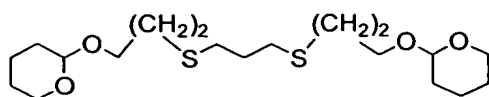
Ic-10

1,9-Bis-(2-oxo-tetrahydropyran-4-yl)-3,7-dithia-nonane



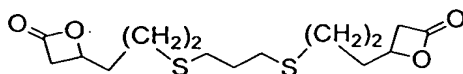
Ic-11

1,9-Bis-(2-oxo-tetrahydropyran-3-yl)-3,7-dithia-nonane



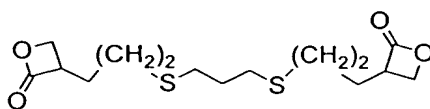
Ic-12

1,11-Bis-(tetrahydro-pyran-2-yloxy)-4,8-lithia-undecane



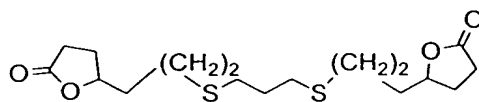
Ic-13

1,11-Bis-(2-oxo-oxetan-3-yl)-4,8-dithia-undecane

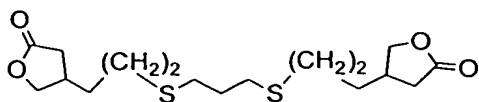


Ic-14

1,11-Bis-(2-oxo-oxetan-3-yl)- 4,8-dithia-undecane

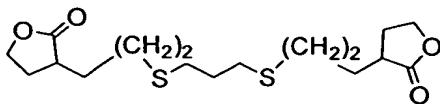
**lc-15**

1,11-Bis-(5-oxo-tetrahydrofuran-2-yl)-4,8-dithia-undecane



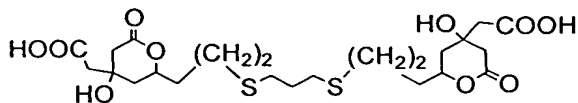
Ic-16

1,11-Bis-(5-oxo-tetrahydrofuran-3-yl)-4,8-dithia-undecane



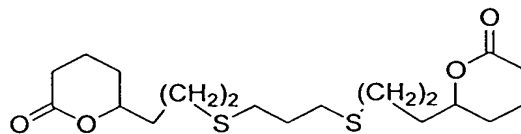
Ic-17

1,11-Bis-(2-oxo-tetrahydrofuran-3-yl)-4,8-dithia-undecane



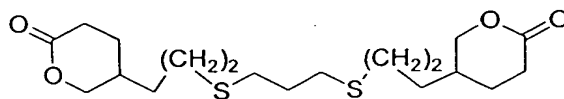
Ic-18

{2-[11-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-4,8-dithia-undecyl]-4-hydroxy-6-oxo-tetrahydropyran-4-yl}-acetic acid



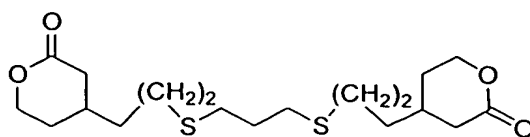
Ic-19

1,11-Bis-(6-oxo-tetrahydropyran-2-yl)-4,8-dithia-undecane



Ic-20

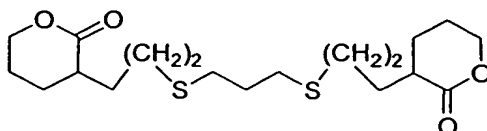
1,11-Bis-(6-oxo-tetrahydropyran-3-yl)-4,8-dithia-undecane



5

Ic-21

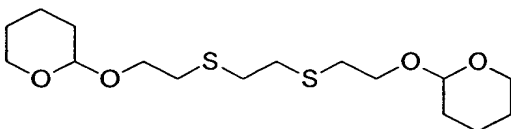
1,11-Bis-(2-oxo-tetrahydropyran-4-yl)-4,8-dithia-undecane



10

Ic-22

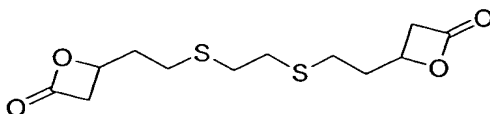
1,11-Bis-(2-oxo-tetrahydropyran-3-yl)-4,8-dithia-undecane



15

Ic-23

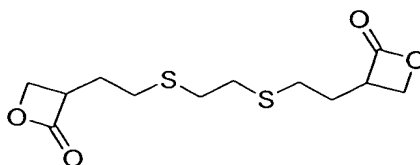
1,8-Bis-(tetrahydropyran-2-yloxy)-3,6-dithio-octane



25

Ic-24

1,8-Bis-(4-oxo-oxetan-2-yl)-3,6-dithio-octane

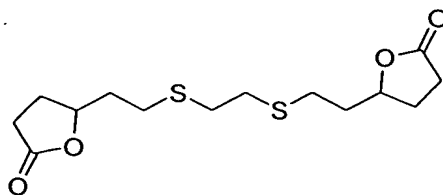


30

Ic-25

1,8-Bis-(2-oxo-oxetan-3-yl)-3,6-dithio-octane

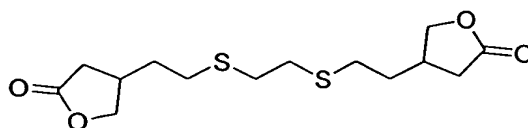
35



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Ic-26

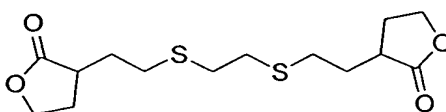
1,8-Bis-(5-oxo-tetrahydro-furan-2-yl)- 3,6-dithio-octane



10

Ic-27

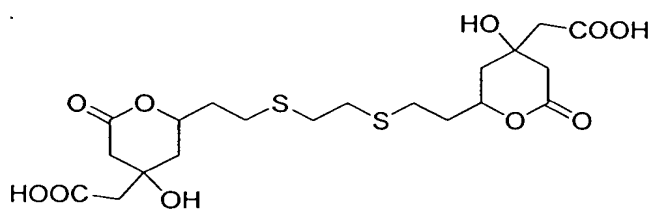
1,8-Bis-(5-oxo-tetrahydro-furan-3-yl)-3,6-dithio-octane



20

Ic-28

1,8-Bis-(2-oxo-tetrahydro-furan-3-yl)-3,6-dithiol-octane



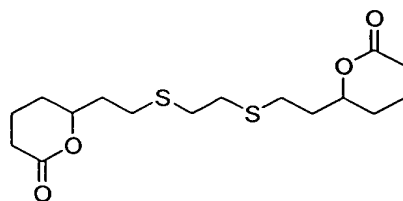
25

Ic-29

[2-(2-{2-[2-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-ethylsulfanyl]-ethylsulfanyl}-ethyl)-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl]-acetic acid

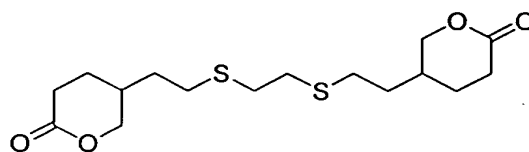
35

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**Ic-30**

1,8-Bis-(6-oxo-tetrahydropyran-2-yl)-3,6-dithio-octane

10

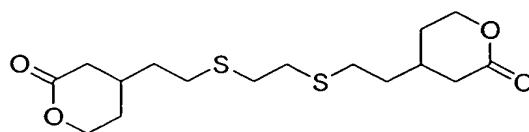


15

Ic-31

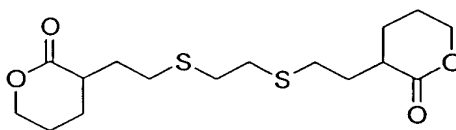
1,8-Bis-(6-oxo-tetrahydropyran-3-yl)-3,6-dithio-octane

20

**Ic-32**

1,8-Bis-(2-oxo-tetrahydropyran-4-yl)-3,6-dithio-octane

25

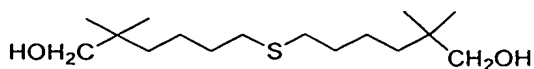


30

Ic-33

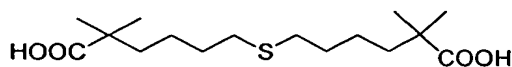
1,8-Bis-(2-oxo-tetrahydropyran-3-yl)-3,6-dithio-octane

35



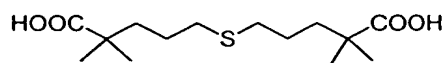
II-1

5 6-(6-Hydroxy-5,5-dimethyl-hexylsulfanyl)-2,2-dimethyl-hexan-1-ol



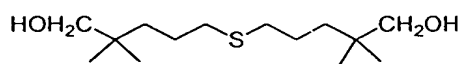
II-2

10 6-(5-Carboxy-5-methyl-hexylsulfanyl)-2,2-dimethyl-hexanoic acid



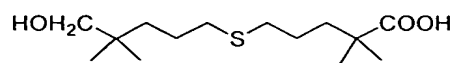
II-3

15 5-(5-Hydroperoxy-4,4-dimethyl-pentylsulfanyl)-2,2-dimethyl-pentanoic acid



II-4

20 5-(5-Hydroxy-4,4-dimethyl-pentylsulfanyl)-2,2-dimethyl-pentan-1-ol

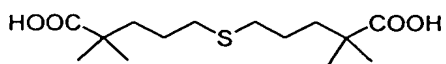


II-5

25 5-(5-Hydroxy-4,4-dimethyl-pentylsulfanyl)-2,2-dimethyl-pentanoic acid

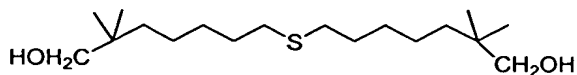
30

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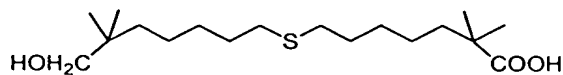
II-6

5 5-(4-Carboxy-4-methyl-pentylsulfanyl)-2,2-dimethyl-pentanoic acid



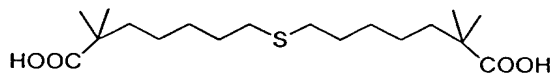
II-7

10 7-(7-Hydroxy-6,6-dimethyl-heptylsulfanyl)-2,2-dimethyl-heptan-1-ol



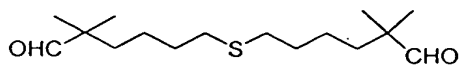
II-8

15 7-(7-Hydroxy-6,6-dimethyl-heptylsulfanyl)-2,2-dimethyl-heptanoic acid



II-9

20 7-(6-Carboxy-6-methyl-heptylsulfanyl)-2,2-dimethyl-heptanoic acid

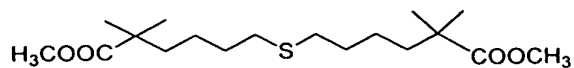


II-10

25 2,2,12,12-Tetramethyl-7-oxo-tridecanedial

30

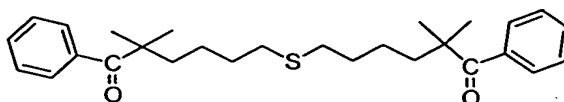
35



5

II-11

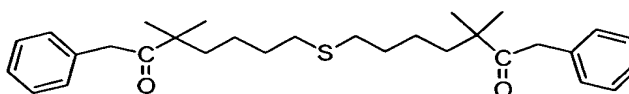
6-(5-Methoxycarbonyl-5-methyl-hexylsulfanyl)-2,2-dimethyl-hexanoic acid methyl ester



10

II-12

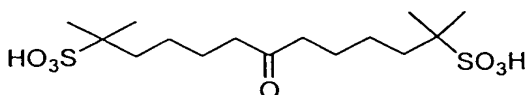
6-(5,5-Dimethyl-6-oxo-6-phenyl-hexylsulfanyl)-2,2-dimethyl-1-phenyl-hexan-1-one



15

II-13

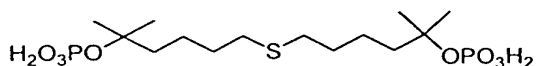
7-(5,5-Dimethyl-6-oxo-7-phenyl-heptylsulfanyl)-3,3-dimethyl-1-phenyl-heptan-2-one



20

II-14

2,12-Dimethyl-7-oxo-tridecane-2,12-disulfonic acid

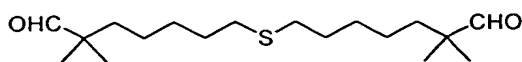


25

II-15

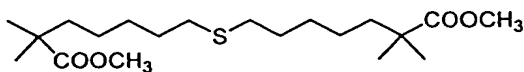
30 Phosphoric acid mono-[1,1-dimethyl-5-(5-methyl-5-phosphonooxy-hexylsulfanyl)-pentyl]
ester

35



II-16

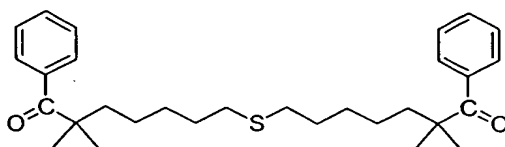
5 2,2,14,14-Tetramethyl-8-oxo-pentadecanedial



10

II-17

7-(6-Methoxycarbonyl-6-methyl-heptylsulfanyl)-2,2-dimethyl-heptanoic acid methyl ester

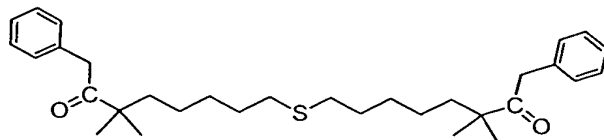


15

II-18

7-(6,6-Dimethyl-7-oxo-7-phenyl-heptylsulfanyl)-2,2-dimethyl-1-phenyl-heptan-1-one

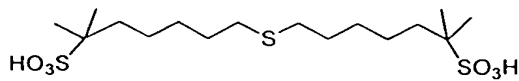
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II-19

8-(6,6-Dimethyl-7-oxo-8-phenyl-octylsulfanyl)-3,3-dimethyl-1-phenyl-octan-2-one

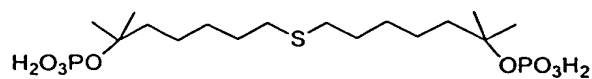


30

II-20

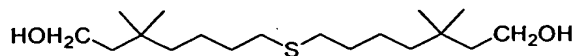
2-Methyl-7-(6-methyl-6-sulfo-heptylsulfanyl)-heptane-2-sulfonic acid

35



II-21

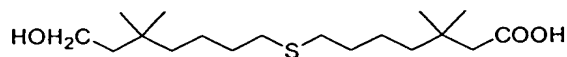
5 Phosphoric acid mono-[1,1-dimethyl-6-(6-methyl-6-phosphonooxy-heptylsulfanyl)-hexyl]
ester



10

II-22

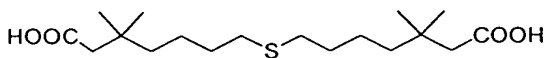
7-(7-Hydroxy-5,5-dimethyl-heptylsulfanyl)-3,3-dimethyl-heptan-1-ol



15

II-23

7-(7-Hydroxy-5,5-dimethyl-heptylsulfanyl)-3,3-dimethyl-heptanoic acid

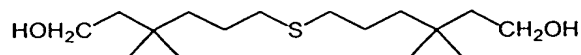


20

II-24

7-(6-Carboxy-5,5-dimethyl-hexylsulfanyl)-3,3-dimethyl-heptanoic acid

25

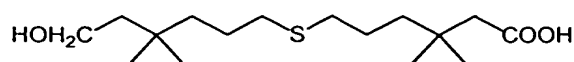


30

II-25

6-(6-Hydroxy-4,4-dimethyl-hexylsulfanyl)-3,3-dimethyl-hexan-1-ol

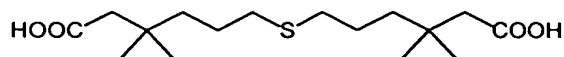
35



II-26

6-(6-Hydroxy-4,4-dimethyl-hexylsulfanyl)-3,3-dimethyl-hexanoic acid

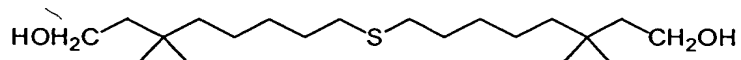
5



II-27

6-(5-Carboxy-4,4-dimethyl-pentylsulfanyl)-3,3-dimethyl-hexanoic acid

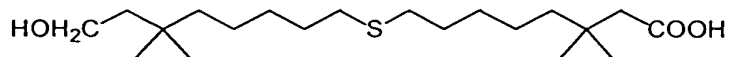
10



II-28

8-(8-Hydroxy-6,6-dimethyl-octylsulfanyl)-3,3-dimethyl-octan-1-ol

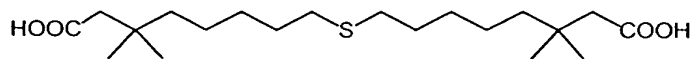
15



II-29

8-(8-Hydroxy-6,6-dimethyl-octylsulfanyl)-3,3-dimethyl-octanoic acid

20



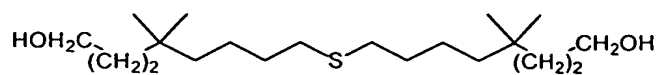
II-30

8-(7-Carboxy-6,6-dimethyl-heptylsulfanyl)-3,3-dimethyl-octanoic acid

25

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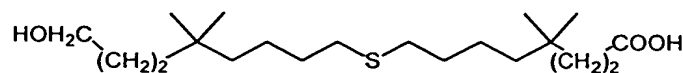
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II-31

8-(7-Hydroxy-5,5-dimethyl-heptylsulfanyl)-4,4-dimethyl-octan-1-ol

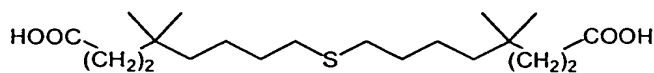
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II-32

8-(8-Hydroxy-5,5-dimethyl-octylsulfanyl)-4,4-dimethyl-octanoic acid

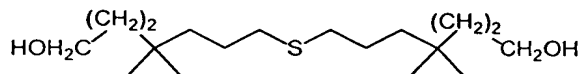
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II-33

8-(6-Carboxy-5,5-dimethyl-hexylsulfanyl)-4,4-dimethyl-octanoic acid

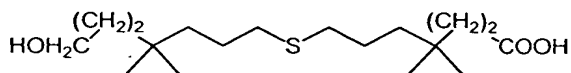
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II-34

7-(7-Hydroxy-4,4-dimethyl-heptylsulfanyl)-4,4-dimethyl-heptan-1-ol

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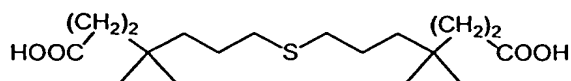
II-35

7-(7-Hydroxy-4,4-dimethyl-heptylsulfanyl)-4,4-dimethyl-heptanoic acid

25

30

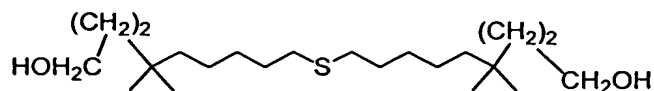
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II-36

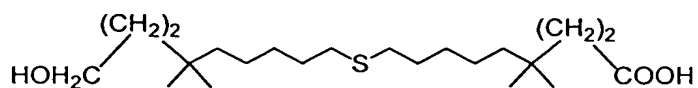
7-(6-Carboxy-4,4-dimethyl-hexylsulfanyl)-4,4-dimethyl-heptanoic acid



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II-37

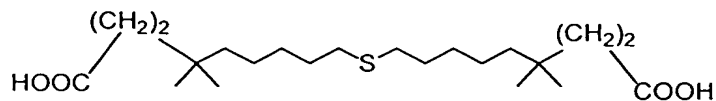
9-(9-Hydroxy-6,6-dimethyl-nonylsulfanyl)-4,4-dimethyl-nonan-1-ol



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II-38

9-(9-Hydroxy-6,6-dimethyl-nonylsulfanyl)-4,4-dimethyl-nonanoic acid

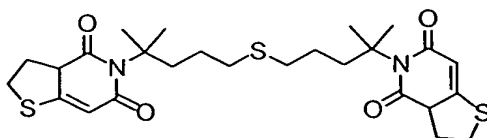


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II-39

25

8-(7-Carboxy-6,6-dimethyl-heptylsulfanyl)-3,3-dimethyl-octanoic acid



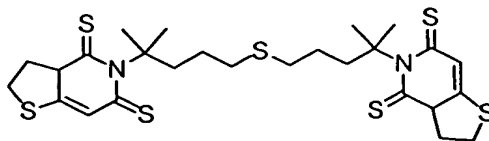
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II-40

5-[1,1-Dimethyl-4-(4-{3,3a-dihydro-4,6-dioxo-2H-thieno[3,2-c]pyridin-5-yl}-4-ethyl-pentane-1-sulfanyl)-butyl]-3,3a-dihydro-2H-thieno [3,2-c]pyridine-4,6-dione

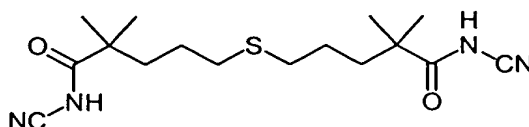
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**II-41**

5-[1,1-Dimethyl-4-(4-{3,3a-dihydro-4,6-dithioxo-2*H*-thieno[3,2-c]pyridin-5-yl}-4-methyl-pentane-1-sulfanyl)-butyl]-3,3a-dihydro-2*H*-thieno[3,2-c]pyridine-4,6-ithione

10

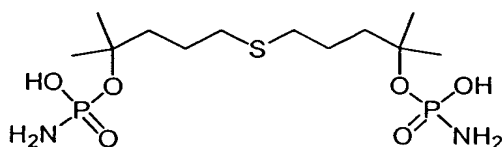


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II-42

5-(4-Cyanocarbamoyl-4-methyl-pentylsulfanyl)-2,2-dimethyl-pentanoic acid cyanamide

20

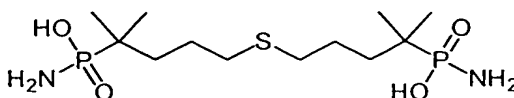
**II-43**

25

Phosphoramidic acid

mono-{4-[4-(amino-hydroxy-phosphoryloxy)-4-methyl-pentylsulfanyl]-1,1-dimethyl-butyl} ester

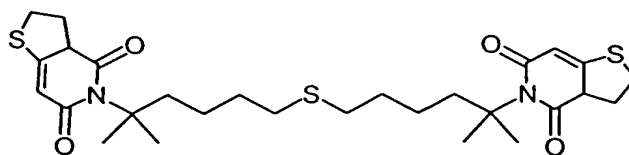
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**II-44**

4-(Amino-hydroxy-phosphoryloxy)-4-methyl-1-(4-[amino-hydroxy-phosphoryloxy]-4-methyl-pentane-1-sulfanyl)-pentane

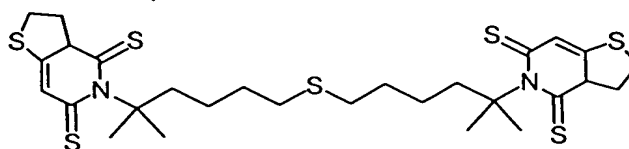
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**II-45**

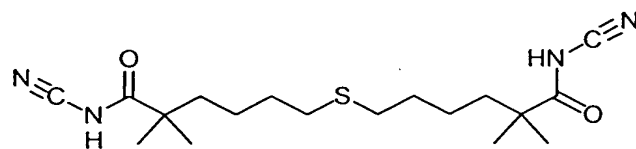
5-[1,1-Dimethyl-5-(5-{3,3a-dihydro-4,6-dioxo-2*H*-thieno[3,2-c] pyridin-5-yl}-5-methyl-hexane-1-sulfanyl)-pentyl]-3,3a-dihydro-2*H*- thieno[3,2-c] pyridine-4,6- dione

10

**II-46**

5-[1,1-Dimethyl-5-(5-{3,3a-dihydro-4,6-dithioxo-2*H*-thieno[3,2-c] pyridin-5-yl}-5-methyl-hexane-1-sulfanyl)-pentyl]-3,3a-dihydro-2*H*- thieno[3,2-c] pyridine-4,6- dithione

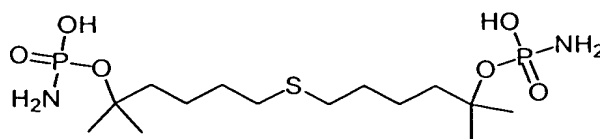
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**II-47**

25

6-(5-Cyanocarbamoyl-5-methyl-hexylsulfanyl)-2,2-dimethyl-hexanoic acid cyanamide

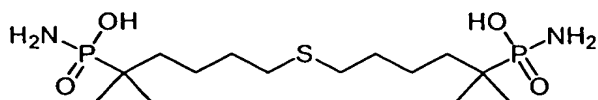
30

**II-48**

Phosphoramidic acid

mono-{5-[5-(amino-hydroxy-phosphoryloxy)-5-methyl-hexylsulfanyl]-1,1-dimethyl-pentyl} ester

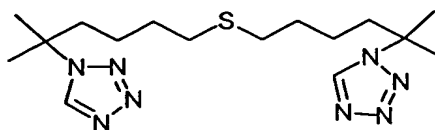
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II-49

5-(Amino-hydroxy-phosphoryloxy)-5-methyl-1-([5-amino-hydroxy-phosphoryloxy]-5-methyl-hexane-1-sulfanyl)-hexane

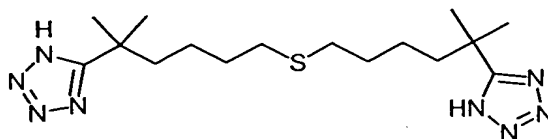


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II-50

1-[1,1-Dimethyl-5-(5-methyl-5-1H-tetrazolyl-hexylsulfanyl)-pentyl]-1H-tetrazole

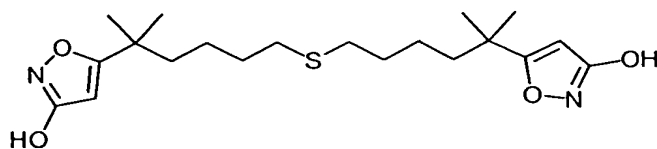
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II-51

5-[1,1-Dimethyl-5-(5-methyl-5-tetrazol-5-yl-hexane-1-sulfanyl)- pentyl]-1*H*-tetrazole

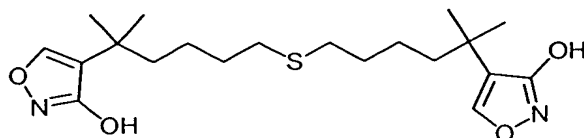


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II-52

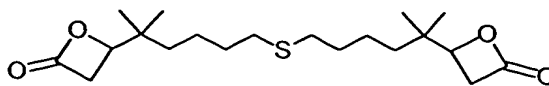
2,12-Bis-(3-hydroxy-isoxazol-5-yl)-2,12-dimethyl-tridecan-7-one

30



II-53

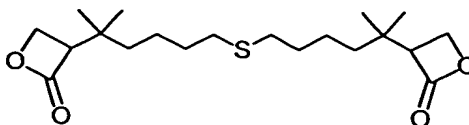
35 4-[1,1-Dimethyl-5-(5-{isoxazol-3-4-yl}-5-methyl-hexane-1-sulfanyl)-pentyl]- isoxazol-3-ol



5

II-54

4-[1,1-Dimethyl-5-(5-{2-oxo-oxetan-4-yl}-5-methyl-hexane-1-sulfanyl)-pentyl]-oxetan-2-one

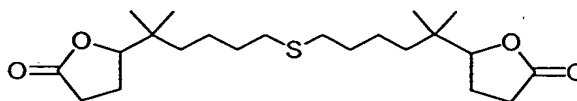


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II-55

3-[1,1-Dimethyl-5-(5-{2-oxo-oxetan-3-yl}-5-methyl-hexane-1-sulfanyl)-pentyl]-oxetan-2-one

15

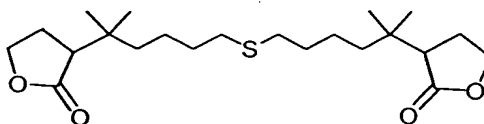


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II-56

5-[1,1-Dimethyl-5-(5-(2-oxo-dihydro-furan-5-yl)-5-methyl-hexane-1-sulfanyl)-pentyl]-dihydro-furan-2-one

25

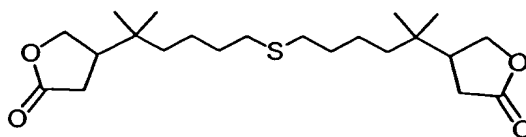


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II-57

3-[1,1-Dimethyl-5-(5-(2-oxo-dihydro-furan-3-yl)-5-methyl-hexane-1-sulfanyl)-pentyl]-dihydro-furan-2-one

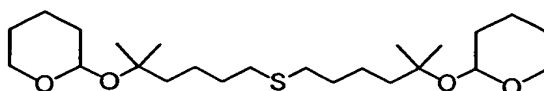
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II-58

4-[1,1-Dimethyl-5-(5-(2-oxo-dihydro-furan-4-yl)-5-methyl-hexane-1-sulfanyl)-
pentyl]-dihydro-furan-2-one

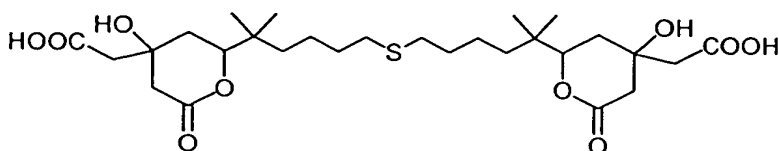


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II-59

2-[1,1-Dimethyl-5-{tetrahydro-pyran-2-oxy}-5-methyl-hexane-1-sulfanyl)-
pentyloxy]-tetrahydro-pyran

15

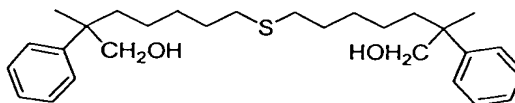


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II-60

(2-{5-[5-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-5-methyl-he xyl
sulfanyl]-1,1-dimethyl-pentyl}-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl)-acetic acid

25

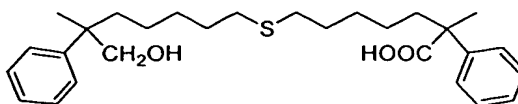


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IIa-1

7-(7-Hydroxy-6-methyl-6-phenyl-heptylsulfanyl)-2-methyl-2-phenyl-heptan-1-ol

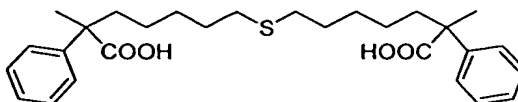
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5

IIa-2

7-(7-Hydroxy-6-methyl-6-phenyl-heptylsulfanyl)-2-methyl-2-phenyl-heptanoic acid

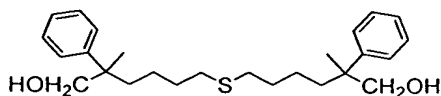


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IIa-3

7-(6-Carboxy-6-phenyl-heptylsulfanyl)-2-methyl-2-phenyl-heptanoic acid

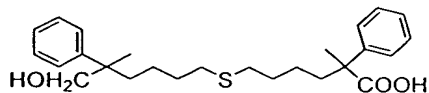
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IIa-4

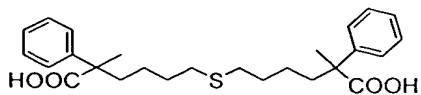
6-(6-Hydroxy-5-methyl-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexan-1-ol



25

IIa-5

6-(6-Hydroxy-5-methyl-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid

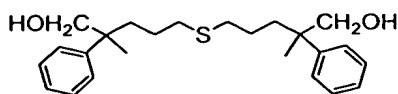


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IIa-6

6-(5-Carboxy-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid

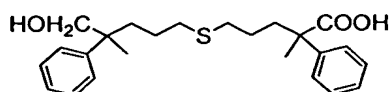
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IIa-7

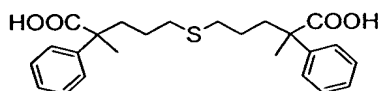
5-(5-Hydroxy-4-methyl-4-phenyl-pentylsulfanyl)-2-methyl-2-phenyl-pentan-1-ol



10

IIa-8

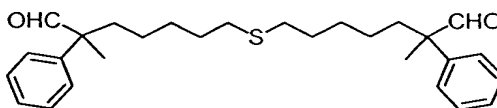
5-(5-Hydroxy-4-methyl-4-phenyl-pentylsulfanyl)-2-methyl-2-phenyl-pentanoic acid



15

IIa-9

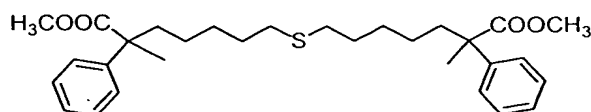
5-(4-Carboxy-4-phenyl-pentylsulfanyl)-2-methyl-2-phenyl-pentanoic acid



25

IIa-10

2-Methyl-7-(6-methyl-7-oxo-6-phenyl-heptylsulfanyl)-2-phenyl-heptanal

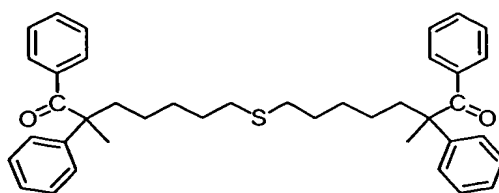


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IIa-11

7-(6-Methoxycarbonyl-6-phenyl-heptylsulfanyl)-2-methyl-2-phenyl-heptanoic acid methyl ester

35

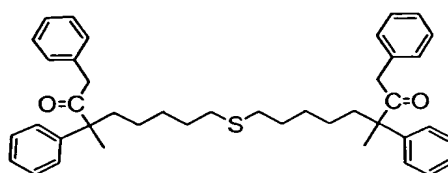


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IIa-12

2-Methyl-7-(6-methyl-7-oxo-6,7-diphenyl-heptylsulfanyl)-1,2-diphenyl-heptan-1-one

10

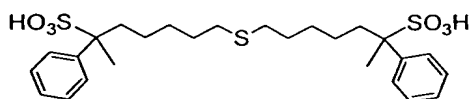


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IIa-13

3-Methyl-8-(6-methyl-7-oxo-6,8-diphenyl-octylsulfanyl)-1,3-diphenyl-octan-2-one

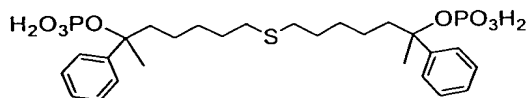
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IIa-14

2-Phenyl-7-(6-phenyl-6-sulfo-heptylsulfanyl)-heptane-2-sulfonic acid



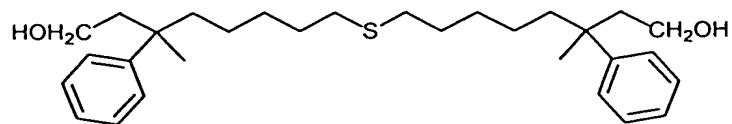
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IIa-15

Phosphoric acid

mono-[1-methyl-1-phenyl-6-(6-phenyl-6-phosphonooxy-heptylsulfanyl)-hexyl] ester

35

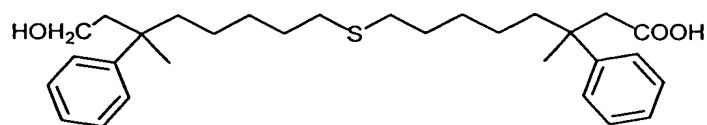


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IIa-16

8-(8-Hydroxy-6-methyl-6-phenyl-octylsulfanyl)-3-methyl-3-phenyl-octan-1-ol

10

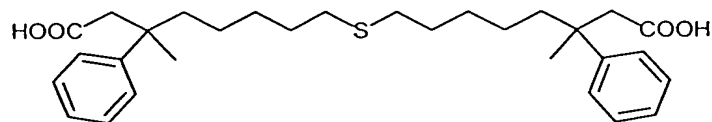


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IIa-17

8-(8-Hydroxy-6-methyl-6-phenyl-octylsulfanyl)-3-methyl-3-phenyl-octanoic acid

20

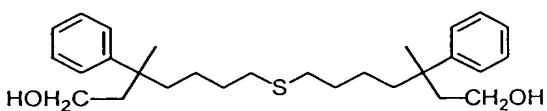


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IIa-18

3,15-Dimethyl-9-oxo-3,15-diphenyl-heptadecanedioic acid

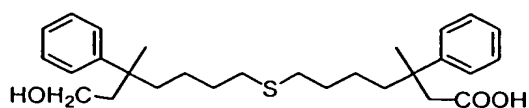
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IIa-19

7-(7-Hydroxy-5-methyl-5-phenyl-heptylsulfanyl)-3-methyl-3-phenyl-heptan-1-ol

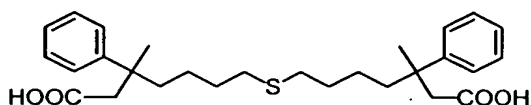
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IIa-20

15-Hydroxy-3,13-dimethyl-8-oxo-3,13-diphenyl-pentadecanoic acid

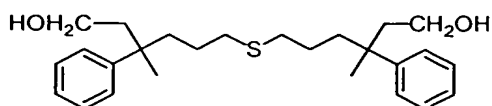


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IIa-21

7-(6-Carboxy-5-methyl-5-phenyl-hexylsulfanyl)-3-methyl-3-phenyl-heptanoic acid

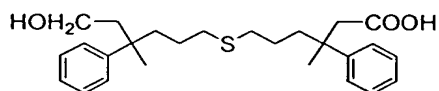
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IIa-22

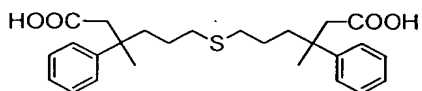
6-(6-Hydroxy-4-methyl-4-phenyl-hexylsulfanyl)-3-methyl-3-phenyl-hexan-1-ol



25

IIa-23

6-(6-Hydroxy-4-methyl-4-phenyl-hexylsulfanyl)-3-methyl-3-phenyl-hexanoic acid

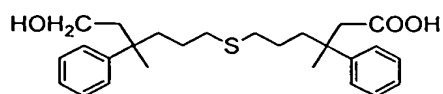


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IIa-24

6-(5-Carboxy-4-methyl-4-phenyl-pentylsulfanyl)-3-methyl-3-phenyl-hexanoic acid

35

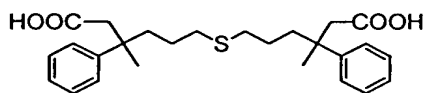


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IIa-25

6-(6-Hydroxy-4-methyl-4-phenyl-hexylsulfanyl)-3-methyl-3-phenyl-hexanoic acid

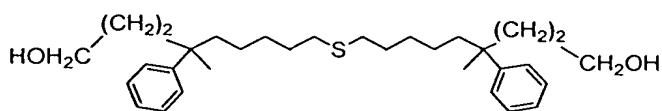
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IIa-26

15

6-(5-Carboxy-4-methyl-4-phenyl-pentylsulfanyl)-3-methyl-3-phenyl-hexanoic acid

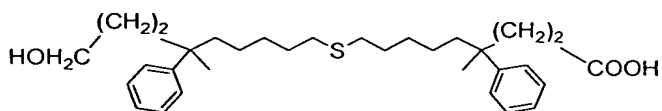


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IIa-27

9-(9-Hydroxy-6-methyl-6-phenyl-nonylsulfanyl)-4-methyl-4-phenyl-nonan-1-ol

25

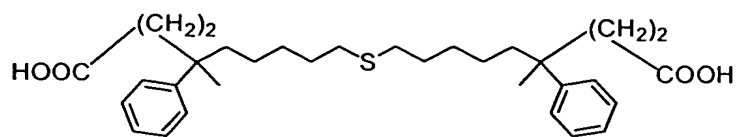


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IIa-28

8-(9-Hydroxy-6-methyl-6-phenyl-nonylsulfanyl)-3-methyl-3-phenyl-octanoic acid

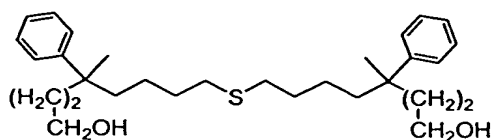
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IIa-29

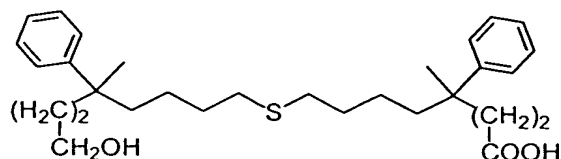
9-(8-Carboxy-6-methyl-6-phenyl-octylsulfanyl)-4-methyl-4-phenyl-nonanoic acid



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IIa-30

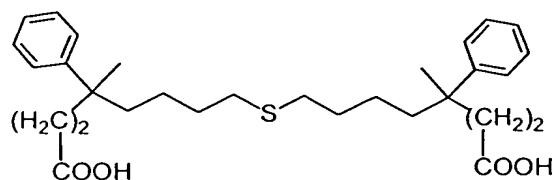
8-(8-Hydroxy-5-methyl-5-phenyl-octylsulfanyl)-4-methyl-4-phenyl-octan-1-ol



20

IIa-31

8-(8-Hydroxy-5-methyl-5-phenyl-octylsulfanyl)-4-methyl-4-phenyl-octanoic acid

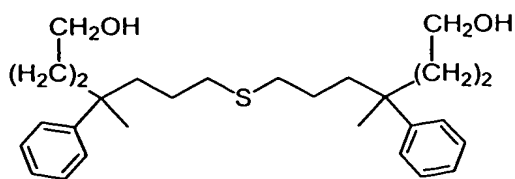


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IIa-32

8-(7-Carboxy-5-methyl-5-phenyl-heptylsulfanyl)-4-methyl-4-phenyl-octanoic acid

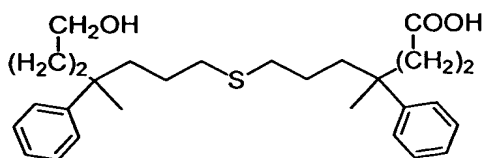
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IIa-33

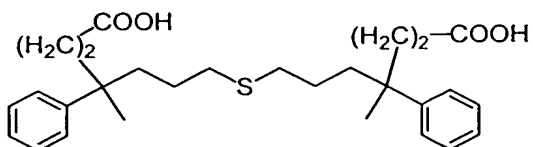
7-(7-Hydroxy-4-methyl-4-phenyl-heptylsulfanyl)-4-methyl-4-phenyl-heptan-1-ol



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IIa-34

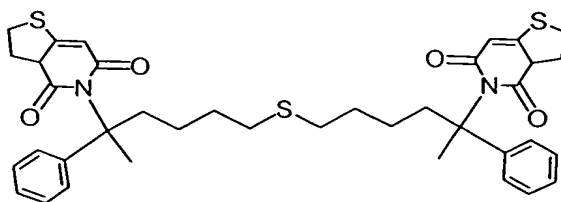
7-(7-Hydroxy-4-methyl-4-phenyl-heptylsulfanyl)-4-methyl-4-phenyl-heptanoic acid



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IIa-35

7-(6-Carboxy-4-methyl-4-phenyl-hexylsulfanyl)-4-methyl-4-phenyl-heptanoic acid



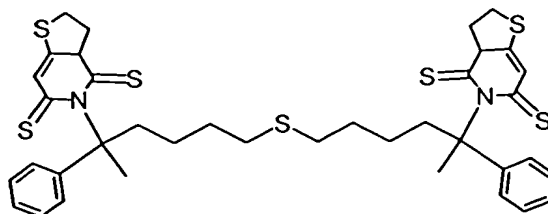
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IIa-36

5-(3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dione)-5-phenyl-1-hexylsulfanyl-5-(3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dione)-5-phenyl-hexane

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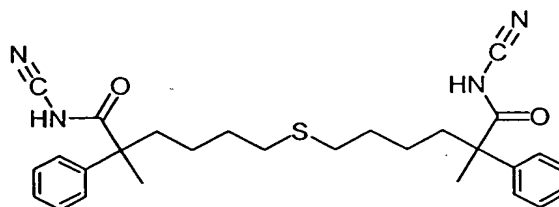


IIa-37

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5-(3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dithione)-5-phenyl-1-hexylsulfanyl-5-(3,3a-Dihydro-2H-thieno[3,2-c]pyridine-4,6-dithione)-5-phenyl-hexane

15

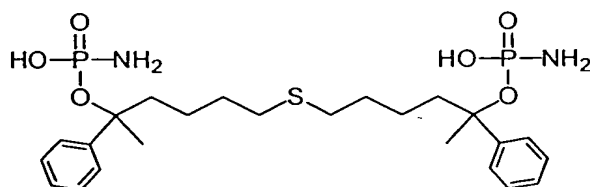


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IIa-38

6-(5-Cyanocarbamoyl-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid cyanamide

25



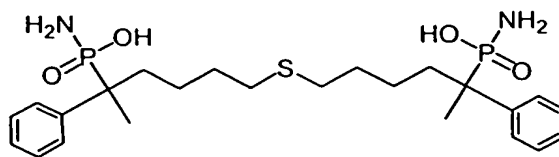
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IIa-39

Phosphoramidic acid

mono-{5-[5-(amino-hydroxy-phosphoryloxy)-5-phenyl-hexylsulfanyl]-1-methyl-1-phenyl-pentyl} ester

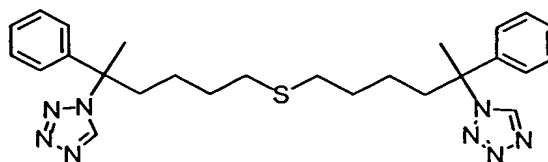
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IIa-40

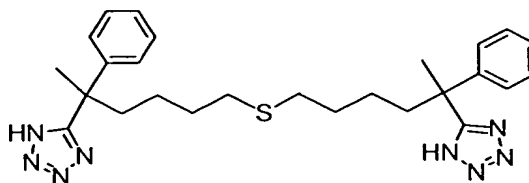
1-(5-[Amino-hydroxy-phosphoryloxy]-5-phenyl-hexane-1-sulfanyl)-
5-[amino-hydroxy-phosphoryloxy]-5-phenylhexane)



10

IIa-41

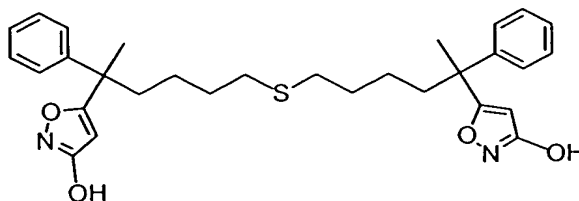
1-(5-Tetrazol-1-yl-5-phenyl-hexylsulfanyl)-5-tetrazol-1-yl-5-phenyl-hexane



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IIa-42

1-(5-Tetrazol-5-yl-5-phenyl-hexylsulfanyl)-5-tetrazol-5-yl-5-phenyl-hexane



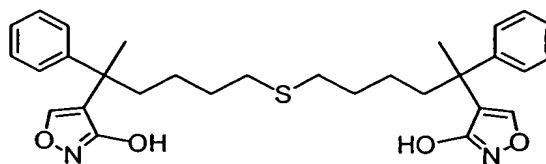
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IIa-43

1(3-Hydroxyisoxazol--5-yl-5-phenyl-hexylsulfanyl)-3-
hydroxyisoxazol--5-yl-5-phenyl-hexane

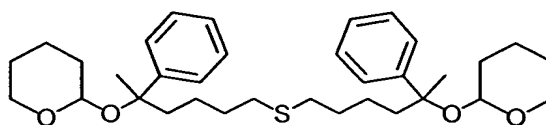
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**IIa-44**

1-(3-Hydroxyisoxazol-4-yl)-5-phenyl-hexylsulfanyl-3-hydroxyisoxazol-4-yl-5-phenyl-hexane

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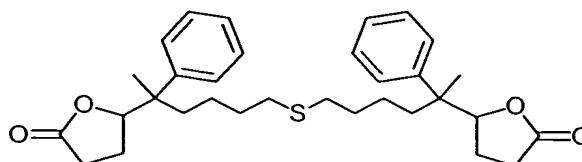


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IIa-45

2-[1-Methyl-1-phenyl-5-(5-{2-hydroxy-tetrahydro-pyranoxy}-5-phenyl-hexane-1-)-pentyloxy]-tetrahydro-pyran

20

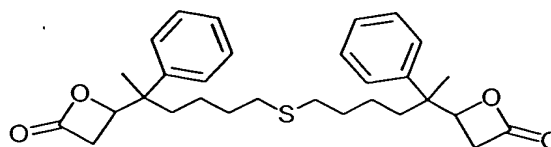


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IIa-46

5-[1-Methyl-1-phenyl-5-(5-{2-oxo-dihydro-furan-5-yl}-5-phenyl-hexane-1-)-pentyl]-dihydro-furan-2-one

30

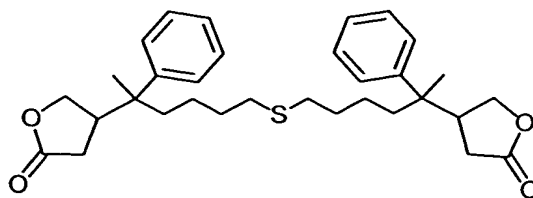


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IIa-47

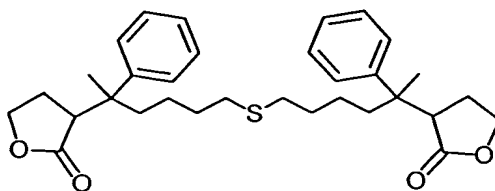
4-[1-Methyl-1-phenyl-5-(5-{2-oxo-oxetan-4-yl}-5-phenyl-hexane-1-sulfanyl)-pentyl]-oxetan-2-one

5

**IIa-48**

4-[1-Methyl-5-(5-dihydro-furan-2-one-5-phenyl-hexylsulfanyl)-1-phenyl-pentyl]-dihydro-fu
ran-2-one

10

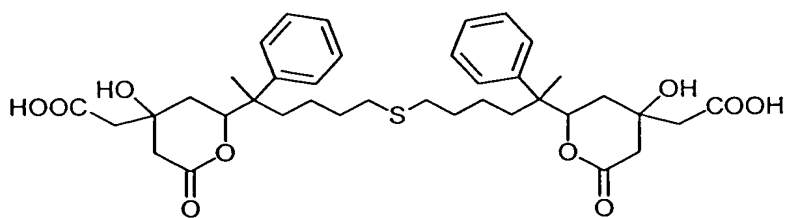


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IIa-49

3-[1-Methyl-5-(5-dihydro-furan-2-one-5-phenyl-hexylsulfanyl)-1-phenyl-pentyl]-dihydro-fu
ran-2-one

20



25

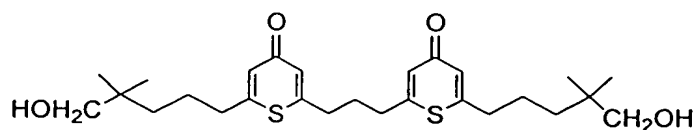
IIa-50

(2-{5-[5-(4-Carboxymethyl-4-hydroxy-6-oxo-tetrahydro-pyran-2-yl)-5-phenyl-hexylsulfanyl
]-1-methyl-1-phenyl-pentyl}-4-hydroxy-6-oxo-tetrahydro-pyran-4-yl)-acetic acid

30

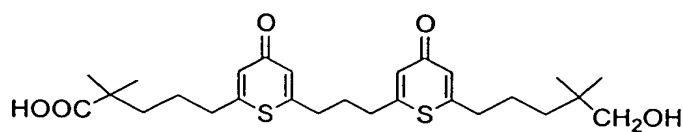
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**III-1**

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-propyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

10

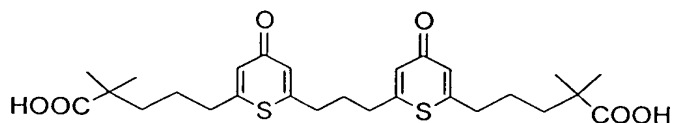


15

III-2

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-propyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

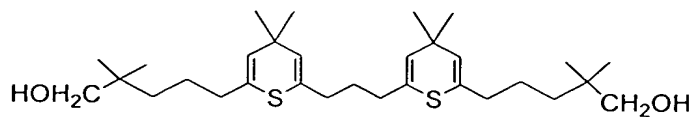
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**III-3**

25

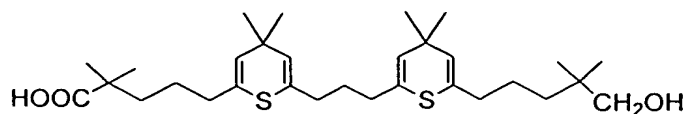
5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-propyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

30

**III-4**

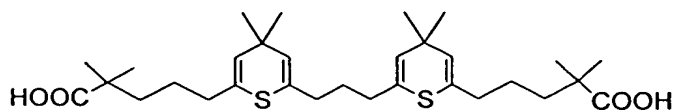
5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-propyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

35



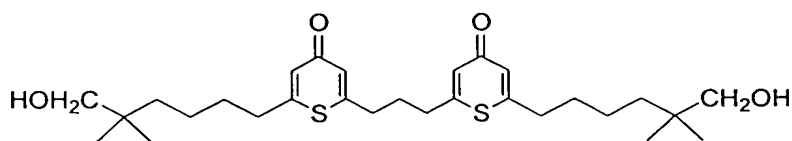
III-5

5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-propyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid



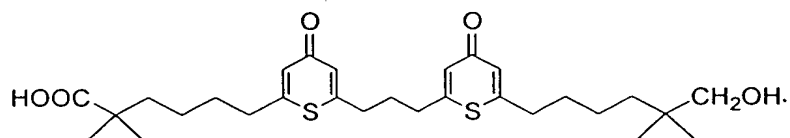
III-6

5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-propyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid



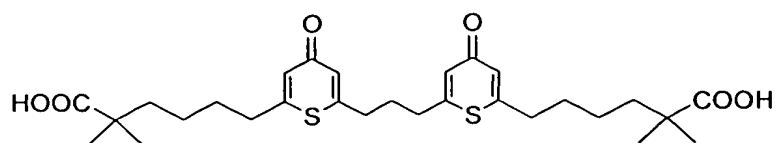
III-7

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-propyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol



III-8

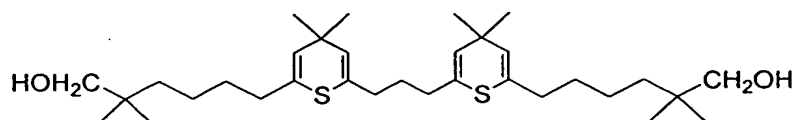
6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-propyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid



5

III-9

6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-propyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

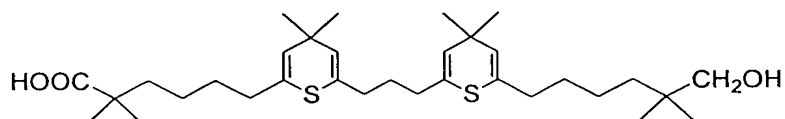


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III-10

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-propyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol

15

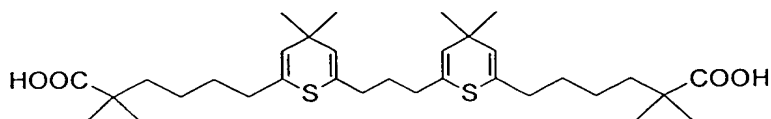


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III-11

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-propyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

25

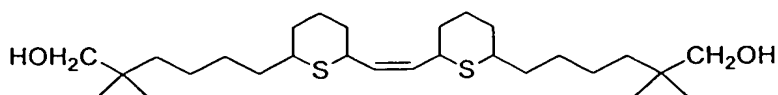


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III-12

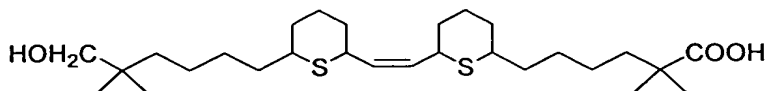
6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-propyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

35



III-13

5 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiopyran-2-yl]-vinyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol

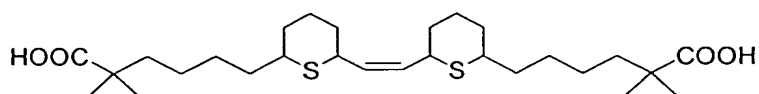


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III-14

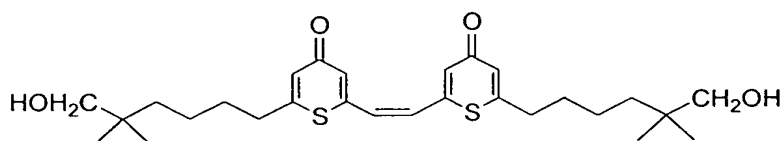
6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiopyran-2-yl]-vinyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

15



III-15

20 6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-tetrahydro-thiopyran-2-yl]-vinyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

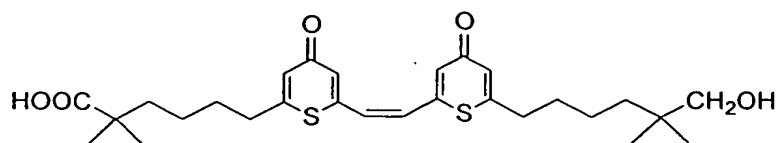


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III-16

30 6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-vinyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol

35

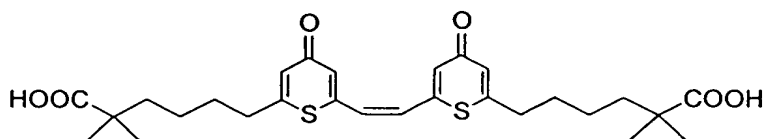


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III-17

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-vinyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

10

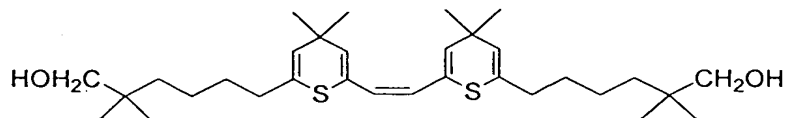


III-18

15

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-vinyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

20

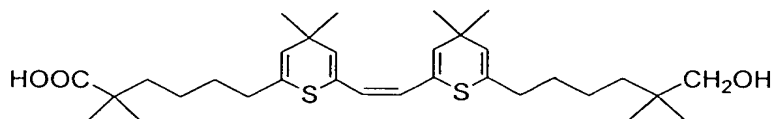


III-19

25

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-vinyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol

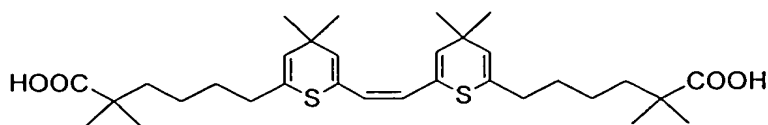
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III-20

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-vinyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

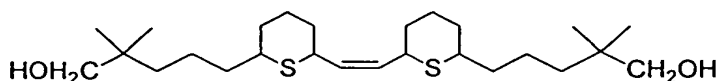
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III-21

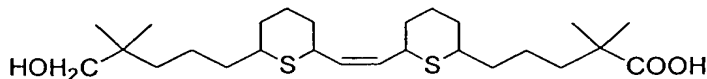
6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-vinyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid



10

III-22

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiopyran-2-yl]-vinyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

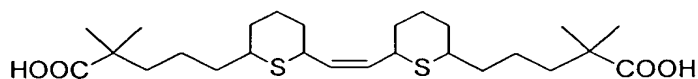


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III-23

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiopyran-2-yl]-vinyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

20

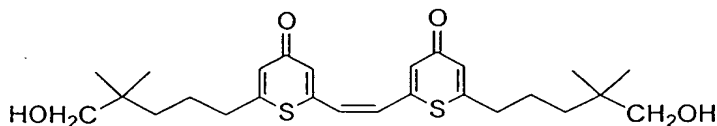


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III-24

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-tetrahydro-thiopyran-2-yl]-vinyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

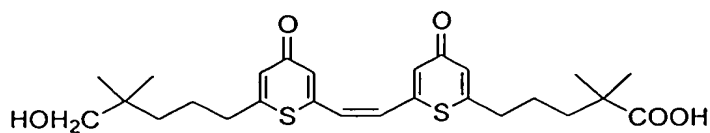
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III-25

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-vinyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

35

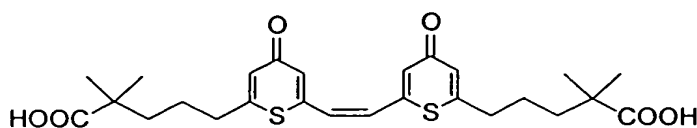


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III-26

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-vinyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

10

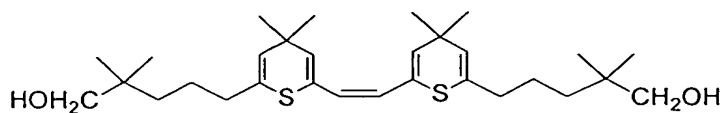


III-27

15

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-vinyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

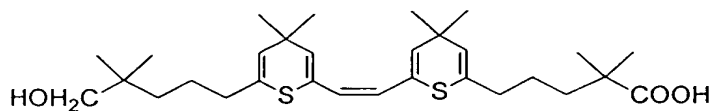
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III-28

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-vinyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

25

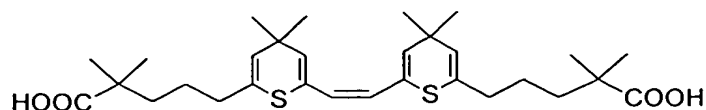


III-29

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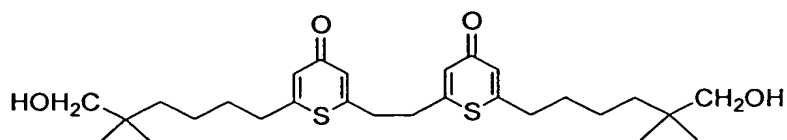
5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-vinyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

35



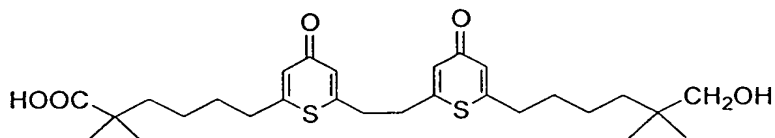
III-30

5- (6- {2- [6- (4- Carboxy-4- methyl- pentyl)- 4,4- dimethyl- 4H- thiopyran- 2- yl]- vinyl}- 4,4- dimethyl- 4H- thiopyran- 2- yl)- 2,2- dimethyl- pentanoic acid



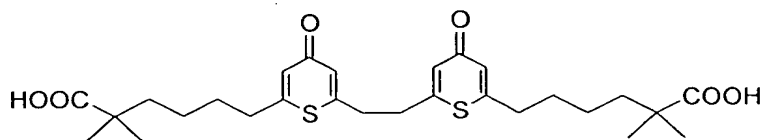
III-31

6- (6- {2- [6- (6- Hydroxy- 5,5- dimethyl- hexyl)- 4- oxo- 4H- thiopyran- 2- yl]- ethyl}- 4- oxo- 4H- thiopyran- 2- yl)- 2,2- dimethyl- hexan- 1- ol



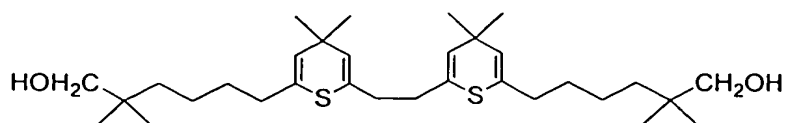
III-32

6- (6- {2- [6- (6- Hydroxy- 5,5- dimethyl- hexyl)- 4- oxo- 4H- thiopyran- 2- yl]- ethyl}- 4- oxo- 4H- thiopyran- 2- yl)- 2,2- dimethyl- hexanoic acid



III-33

6- (6- {2- [6- (5- Carboxy- 5- methyl- hexyl)- 4- oxo- 4H- thiopyran- 2- yl]- ethyl}- 4- oxo- 4H- thiopyran- 2- yl)- 2,2- dimethyl- hexanoic acid

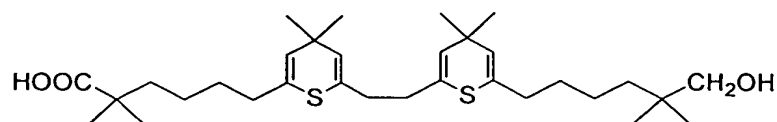


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III-34

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-ethyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol

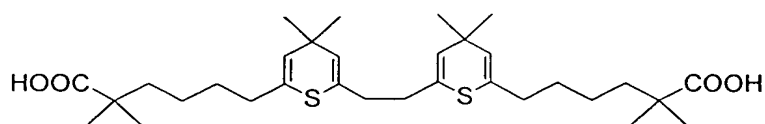
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III-35

15

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-ethyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

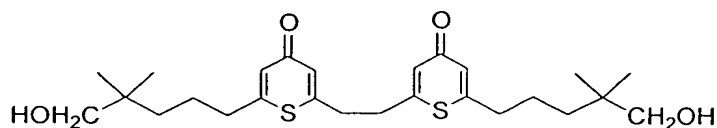


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III-36

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-ethyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

25

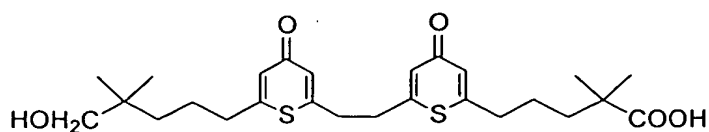


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III-37

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-ethyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

35

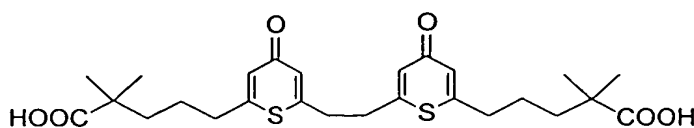


5

III-38

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-ethyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

10

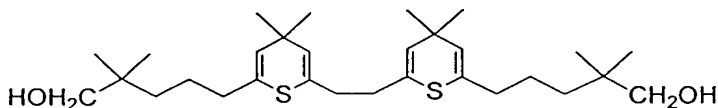


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III-39

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-ethyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

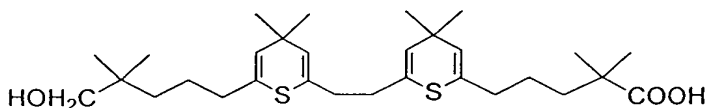
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III-40

25

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-ethyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

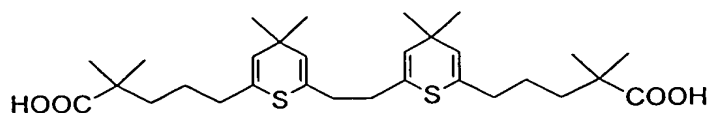


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III-41

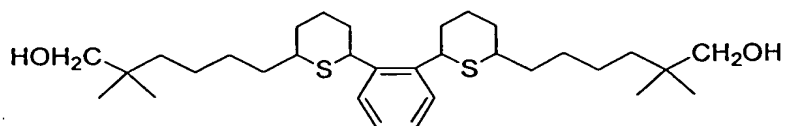
5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-ethyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

35



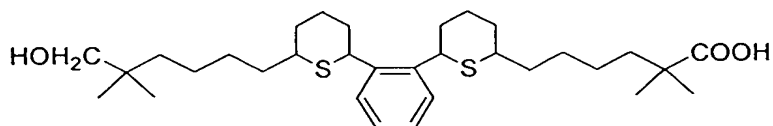
III-42

5- (6- {2- [6- (4- Carboxy-4- methyl- pentyl)-4,4- dimethyl-4H- thiopyran-2- yl]-ethyl}-4,4- dimethyl-4H- thiopyran-2- yl)-2,2- dimethyl- pentanoic acid



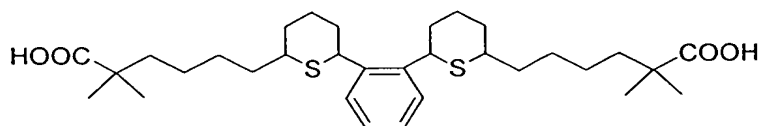
III-43

6- (6- {2- [6- (6- Hydroxy-5,5- dimethyl- hexyl)-tetrahydro- thiopyran-2- yl]-phenyl}-tetrahydro- thiopyran-2- yl)-2,2- dimethyl- hexan-1- ol



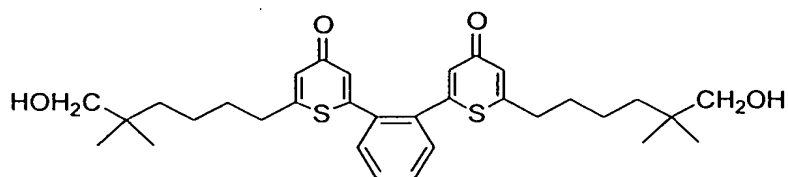
III-44

6- (6- {2- [6- (6- Hydroxy-5,5- dimethyl- hexyl)-tetrahydro- thiopyran-2- yl]-phenyl}-tetrahydro- thiopyran-2- yl)-2,2- dimethyl- hexanoic acid



III-45

6- (6- {2- [6- (6- Carboxy-5,5- dimethyl- hexyl)-tetrahydro- thiopyran-2- yl]-phenyl}-tetrahydro- thiopyran-2- yl)-2,2- dimethyl- hexanoic acid

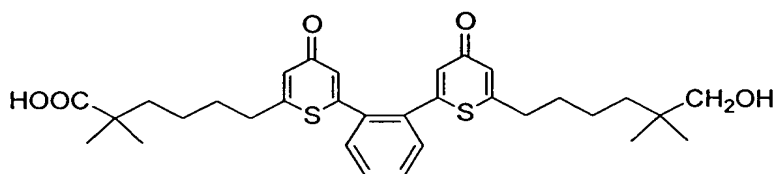


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III-46

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-phenyl}-tetrahydrothiopyran-2-yl)-2,2-dimethyl-hexan-1-ol

10

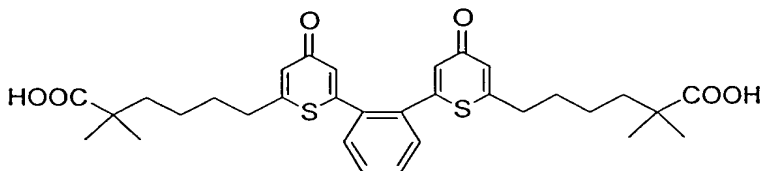


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III-47

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-phenyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

20

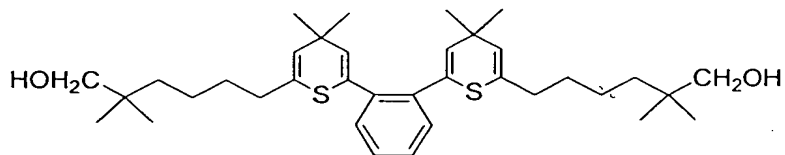


25

III-48

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4-oxo-4H-thiopyran-2-yl]-phenyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

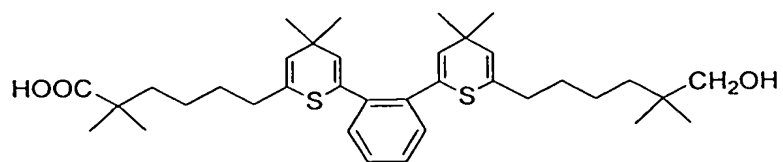
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III-49

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-phenyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol

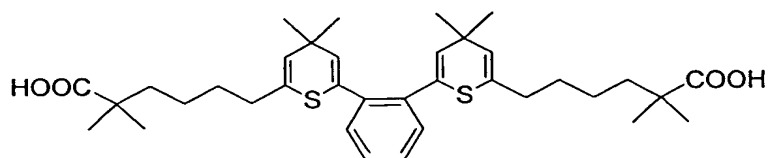


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III-50

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-phenyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

10

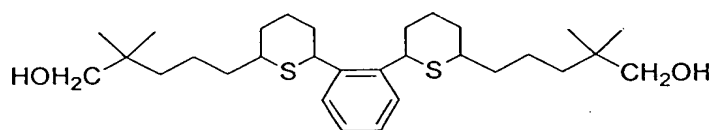


III-51

15

6-(6-{2-[6-(5-Carboxy-5-methyl-hexyl)-4,4-dimethyl-4H-thiopyran-2-yl]-phenyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid

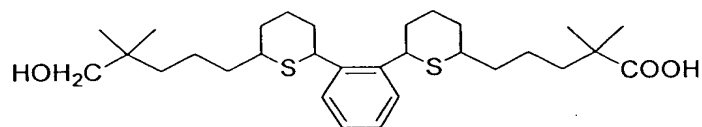
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III-52

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiopyran-2-yl]-phenyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

25

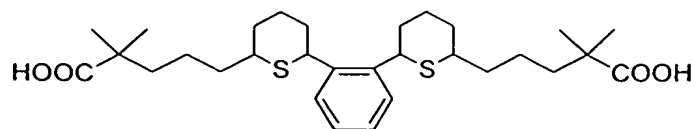


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III-53

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiopyran-2-yl]-phenyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

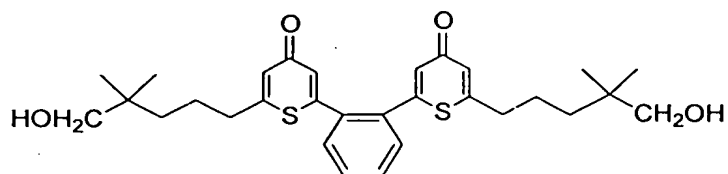
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III-54

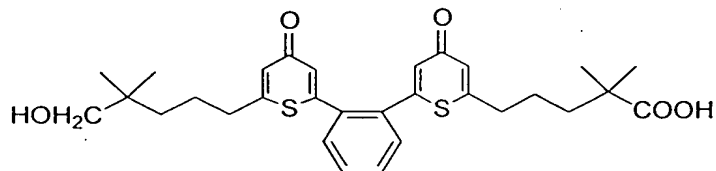
5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-tetrahydro-thiopyran-2-yl]-phenyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid



10

III-55

5-(6-{2-[6-(5-Hydroxy-4-methyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-phenyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol



20

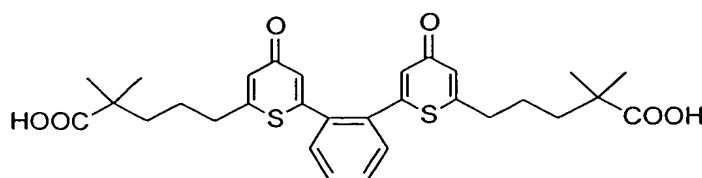
III-56

5-(6-{2-[6-(5-Hydroxy-4-methyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-phenyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

25

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35

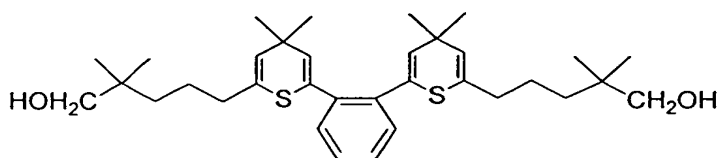


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III-57

5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4-oxo-4H-thiopyran-2-yl]-phenyl}-4-oxo-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

10

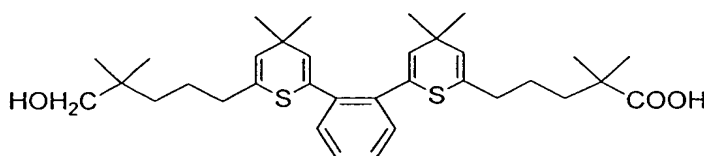


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III-58

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-phenyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol

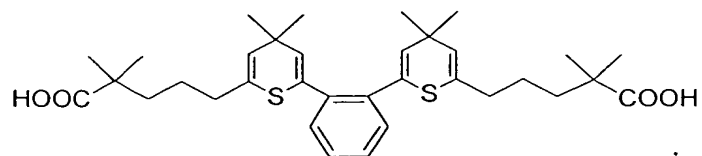
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III-59

5-(6-{2-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-phenyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

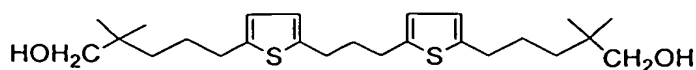
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III-60

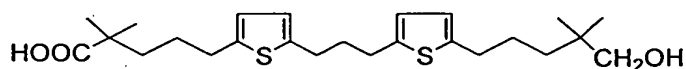
5-(6-{2-[6-(4-Carboxy-4-methyl-pentyl)-4,4-dimethyl-4H-thiopyran-2-yl]-phenyl}-4,4-dimethyl-4H-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

35



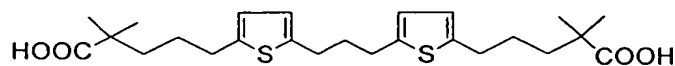
III-61

5- (5- {3- [5- (5-Hydroxy-4,4-dimethyl-pentyl)-thiophen-2-yl]-propyl} -thiophen-2-yl)-2,2-dimethyl-pentan-1-ol



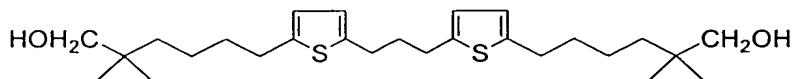
III-62

5- (5- {3- [5- (5-Hydroxy-4,4-dimethyl-pentyl)-thiophen-2-yl]-propyl} -thiophen-2-yl)-2,2-dimethyl-pentanoic acid



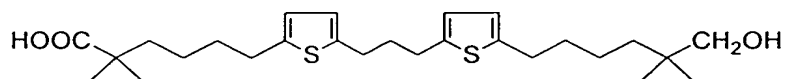
III-63

5- (5- {3- [5- (4-Carboxy-4-methyl-pentyl)-thiophen-2-yl]-propyl} -thiophen-2-yl)-2,2-dimethyl-pentanoic acid



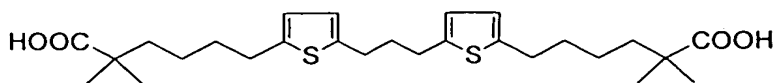
III-64

6- (5- {3- [5- (6-Hydroxy-5,5-dimethyl-hexyl)-thiophen-2-yl]-propyl} -thiophen-2-yl)-2,2-dimethyl-hexan-1-ol



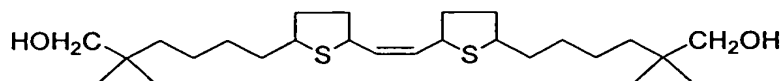
III-65

6- (5- {3- [5- (6-Hydroxy-5,5-dimethyl-hexyl)-thiophen-2-yl]-propyl} -thiophen-2-yl)-2,2-dimethyl-hexanoic acid



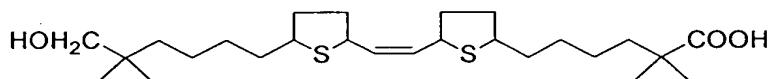
III-66

5 6-(5-{3-[5-(5-Carboxy-5-methyl-hexyl)-thiophen-2-yl]-propyl}-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



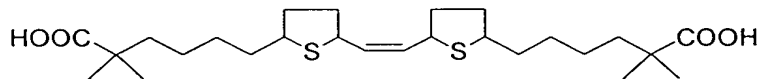
III-67

10 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-hexan-1-ol



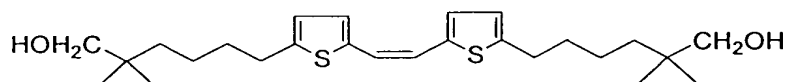
III-68

15 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



III-69

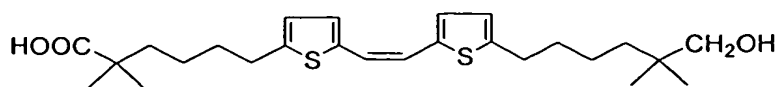
20 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



III-70

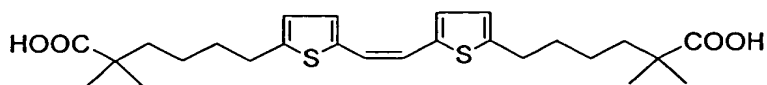
30 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-hexan-1-ol

35



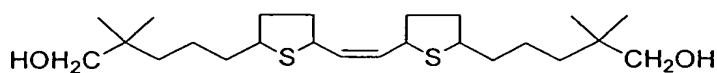
III-71

5 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



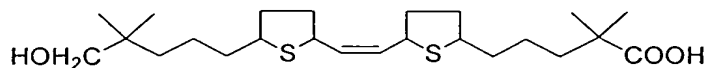
III-72

10 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



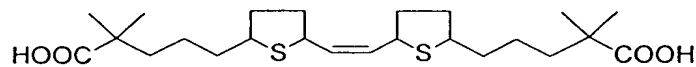
III-73

15 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-pentan-1-ol



III-74

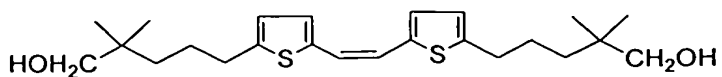
20 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-pentanoic acid



III-75

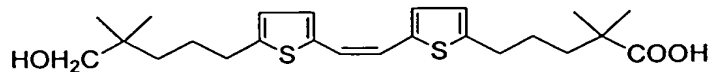
25 5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-pentanoic acid

35



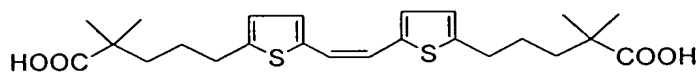
III-76

5 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-pentan-1-ol



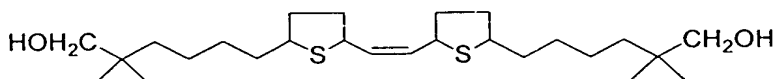
III-77

10 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-pentanoic acid



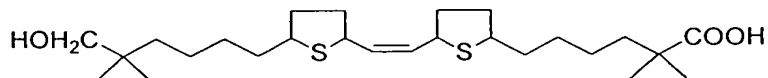
III-78

15 5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-pentanoic acid



III-79

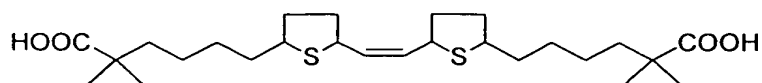
20 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-hexan-1-ol



III-80

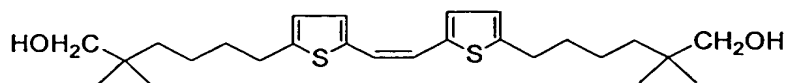
30 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-hexanoic acid

35



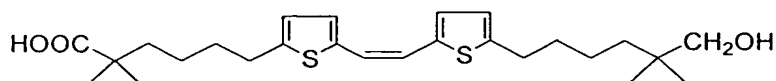
III-81

5 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-tetrahydro-thiophen-2-yl]-vinyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



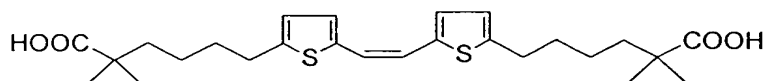
III-82

10 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-hexan-1-ol



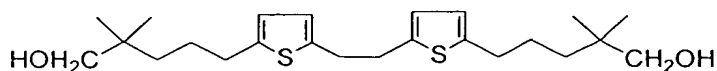
III-83

15 6-(5-{2-[5-(6-Hydroxy-5,5-dimethyl-hexyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



III-84

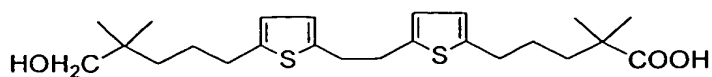
25 6-(5-{2-[5-(5-Carboxy-5-methyl-hexyl)-thiophen-2-yl]-vinyl}-thiophen-2-yl)-2,2-dimethyl-hexanoic acid



III-85

30 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-thiophen-2-yl]-ethyl}-thiophen-2-yl)-2,2-dimethyl-pentan-1-ol

35



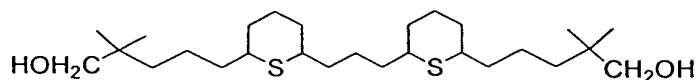
III-86

5 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-thiophen-2-yl]-ethyl}-thiophen-2-yl)-2,2-dimethyl-pentanoic acid



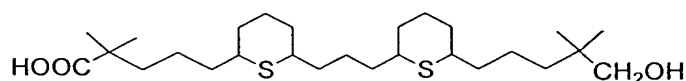
III-87

10 5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-thiophen-2-yl]-ethyl}-thiophen-2-yl)-2,2-dimethyl-pentanoic acid



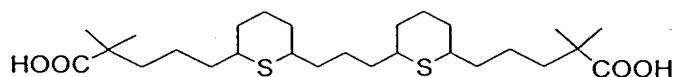
IIIa-1

15 5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiopyran-2-yl]-propyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentan-1-ol



IIIa-2

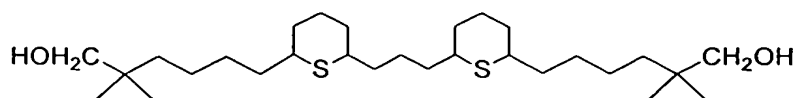
20 5-(6-{3-[6-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiopyran-2-yl]-propyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid



IIIa-3

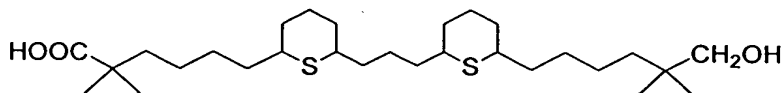
30 5-(6-{3-[6-(4-Carboxy-4-methyl-pentyl)-tetrahydro-thiopyran-2-yl]-propyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-pentanoic acid

35



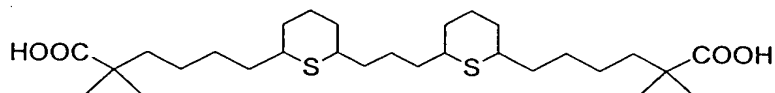
IIIa-4

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiopyran-2-yl]-propyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol



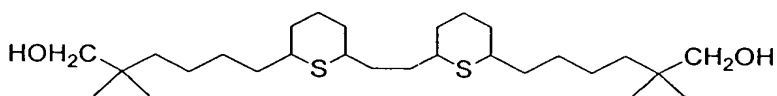
IIIa-5

6-(6-{3-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiopyran-2-yl]-propyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid



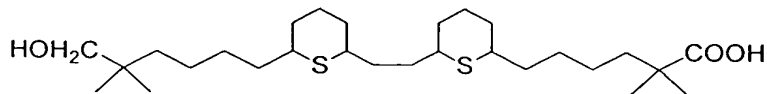
IIIa-6

6-(6-{3-[6-(5-Carboxy-5-methyl-hexyl)-tetrahydro-thiopyran-2-yl]-propyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid



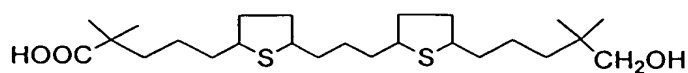
IIIa-7

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiopyran-2-yl]-ethyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexan-1-ol



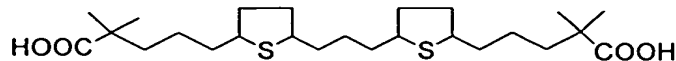
IIIa-8

6-(6-{2-[6-(6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiopyran-2-yl]-ethyl}-tetrahydro-thiopyran-2-yl)-2,2-dimethyl-hexanoic acid



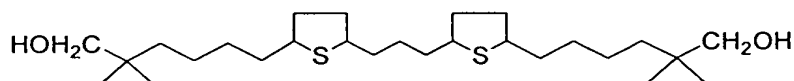
IIIa-14

5- (5- {3- [5- (5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiophen-2-yl]-propyl}-tetrahydro-
thiophen-2-yl)-2,2-dimethyl-pentanoic acid



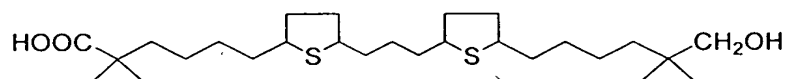
IIIa-15

5- (5- {3- [5- (4-Carboxy-4-methyl-pentyl)-tetrahydro-thiophen-2-yl]-propyl}-tetrahydro-
thiophen-2-yl)-2,2-dimethyl-pentanoic acid



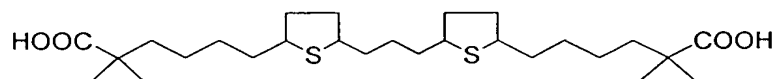
IIIa-16

6- (5- {3- [5- (6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiophen-2-yl]-propyl}-tetrahydro-
thiophen-2-yl)-2,2-dimethyl-hexan-1-ol



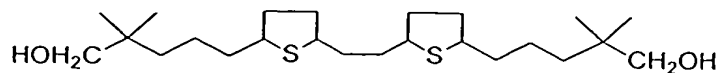
IIIa-17

6- (5- {3- [5- (6-Hydroxy-5,5-dimethyl-hexyl)-tetrahydro-thiophen-2-yl]-propyl}-tetrahydro-
thiophen-2-yl)-2,2-dimethyl-hexanoic acid



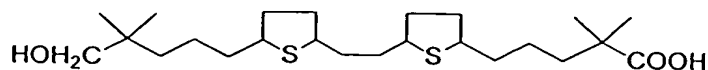
IIIa-18

6- (5- {3- [5- (5-Carboxy-5-methyl-hexyl)-tetrahydro-thiophen-2-yl]-propyl}-tetrahydro-
thiophen-2-yl)-2,2-dimethyl-hexanoic acid



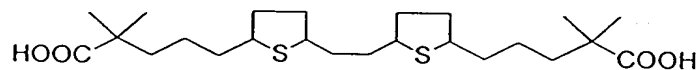
IIIa-19

5 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiophen-2-yl]-ethyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-pentan-1-ol



IIIa-20

10 5-(5-{2-[5-(5-Hydroxy-4,4-dimethyl-pentyl)-tetrahydro-thiophen-2-yl]-ethyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-pentanoic acid



IIIa-21

15 5-(5-{2-[5-(4-Carboxy-4-methyl-pentyl)-tetrahydro-thiophen-2-yl]-ethyl}-tetrahydro-thiophen-2-yl)-2,2-dimethyl-pentanoic acid

The present invention may be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting embodiments of the invention.

3.1 Brief Description of the Drawings

5 FIGS. 1a through 1t are preferred compounds of the invention.

 FIG. 2 illustrates the Effect of One Week Daily Oral Gavage Treatment on Lipoprotein Total Cholesterol in Chow-Fed male Sprague-Dawley Rats.

 FIG. 3 is a graph of Effect of One Week Daily Oral Gavage Treatment on Serum Lipids in Chow-Fed Male Sprague-Dawley Rats

10 FIG. 4 is a graph of the Effects of Two Weeks of Daily Oral Gavage Treatment on Lipoprotein Total Cholesterol in Chow-Fed Obese Female Zucker Rats.

 FIG. 5 is a table of the Effects of Two Weeks of Daily Oral Gavage Treatment in Chow-Fed Obese Female Zucker Rats.

15 4. Detailed Description of the Invention

 The present invention provides novel compounds useful for treating or preventing aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (*e.g.*, Syndrome X), a thrombotic disorder, inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (*e.g.*, Crohn's Disease, ulcerative colitis), arthritis (*e.g.*, 25 rheumatoid arthritis, osteoarthritis), autoimmune disease (*e.g.*, systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism.

30 In this regard, the compounds of the invention are particularly useful when incorporated in a pharmaceutical composition having a carrier, excipient, diluent, or a mixture thereof. A composition of the invention need not contain additional ingredients, such as an excipient, other than a compound of the invention. Accordingly, in one

embodiment, the compositions of the invention can omit pharmaceutically acceptable excipients and diluents and can be delivered in a gel cap or drug delivery device. Accordingly, the present invention provides methods for treating or preventing aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (*e.g.*, Syndrome X), a thrombotic disorder, inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (*e.g.*, Crohn's Disease, ulcerative colitis), arthritis (*e.g.*, rheumatoid arthritis, osteoarthritis), autoimmune disease (*e.g.*, systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism, comprising administering to a patient in need thereof a therapeutically effective amount of a compound or composition of the invention.

In certain embodiments of the invention, a compound of the invention is administered in combination with another therapeutic agent. The other therapeutic agent provides additive or synergistic value relative to the administration of a compound of the invention alone. The therapeutic agent can be a lovastatin; a thiazolidinedione or fibrate; a bile-acid-binding-resin; a niacin; an anti-obesity drug; a hormone; a tyroproline; a sulfonylurea-based drug; a biguanide; an α -glucosidase inhibitor; an apolipoprotein A-I agonist; apolipoprotein E; a phosphodiesterase type-5 inhibitor drug; a cardiovascular drug; an HDL-raising drug; an HDL enhancer; or a regulator of the apolipoprotein A-I, apolipoprotein A-IV and/or apolipoprotein genes.

4.1 Definitions and Abbreviations

Apo(a): apolipoprotein(a)
Apo A-I: apolipoprotein A-I
Apo B: apolipoprotein B
Apo E: apolipoprotein E
FH: Familial hypercholesterolemia
FCH: Familial combined hyperlipidemia

GDM: Gestational diabetes mellitus
HDL: High density lipoprotein
IDL: Intermediate density lipoprotein
IDDM: Insulin dependent diabetes mellitus

5 LDH: Lactate dehydrogenase
LDL: Low density lipoprotein
Lp(a): Lipoprotein (a)
MODY: Maturity onset diabetes of the young
NIDDM: Non-insulin dependent diabetes mellitus
10 PPAR: Peroxisome proliferator activated receptor
RXR: Retinoid X receptor
VLDL: Very low density lipoprotein

The compounds of the invention can contain one or more chiral centers and/or double bonds and, therefore, exist as stereoisomers, such as double-bond isomers (*i.e.*,
15 geometric isomers), enantiomers, or diastereomers. According to the invention, the chemical structures depicted herein, and therefore the compounds of the invention, encompass all of the corresponding compound's enantiomers and stereoisomers, that is, both the stereomerically pure form (*e.g.*, geometrically pure, enantiomerically pure, or diastereomerically pure) and enantiomeric and stereoisomeric mixtures.

20 A compound of the invention is considered optically active or enantiomerically pure (*i.e.*, substantially the R-form or substantially the S-form) with respect to a chiral center when the compound is about 90% ee (enantiomeric excess) or greater, preferably, equal to or greater than 95% ee with respect to a particular chiral center. A compound of the invention is considered to be in enantiomerically-enriched form when the compound has an
25 enantiomeric excess of greater than about 1% ee, preferably greater than about 5% ee, more preferably, greater than about 10% ee with respect to a particular chiral center. A compound of the invention is considered diastereomerically pure with respect to multiple chiral centers when the compound is about 90% de (diastereomeric excess) or greater, preferably, equal to or greater than 95% de with respect to a particular chiral center. A
30 compound of the invention is considered to be in diastereomerically-enriched form when the compound has an diastereomeric excess of greater than about 1% de, preferably greater than about 5% de, more preferably, greater than about 10% de with respect to a particular chiral center. As used herein, a racemic mixture means about 50% of one enantiomer and

about 50% of is corresponding enantiomer relative to all chiral centers in the molecule. Thus, the invention encompasses all enantiomerically-pure, enantiomerically-enriched, diastereomerically pure, diastereomerically enriched, and racemic mixtures of compounds of Formulas I through III.

5 Enantiomeric and stereoisomeric mixtures can be resolved into their component enantiomers or stereoisomers by well known methods, such as chiral-phase gas chromatography, chiral-phase high performance liquid chromatography, crystallizing the compound as a chiral salt complex, or crystallizing the compound in a chiral solvent. Enantiomers and stereoisomers can also be obtained from stereomerically- or
10 enantiomerically-pure intermediates, reagents, and catalysts by well known asymmetric synthetic methods.

 The compounds of the invention are defined herein by their chemical structures and/or chemical names. Where a compound is referred to by both a chemical structure and a chemical name, and the chemical structure and chemical name conflict, the chemical
15 structure is determinative of the compound's identity.

 When administered to a patient, *e.g.*, to an animal for veterinary use or for improvement of livestock, or to a human for clinical use, the compounds of the invention are administered in isolated form or as the isolated form in a pharmaceutical composition. As used herein, "isolated" means that the compounds of the invention are separated from
20 other components of either (a) a natural source, such as a plant or cell, preferably bacterial culture, or (b) a synthetic organic chemical reaction mixture. Preferably, via conventional techniques, the compounds of the invention are purified. As used herein, "purified" means that when isolated, the isolate contains at least 95%, preferably at least 98%, of a single ether compound of the invention by weight of the isolate.

25 The phrase "pharmaceutically acceptable salt(s)," as used herein includes, but are not limited to, salts of acidic or basic groups that may be present in the compounds of the invention. Compounds that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds are those that form
30 non-toxic acid addition salts, *i.e.*, salts containing pharmacologically acceptable anions, including, but not limited to, sulfuric, citric, maleic, acetic, oxalic, hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, oleate, tannate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate,

glucuronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate (*i.e.*, 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)) salts. Compounds of the invention that include an amino moiety also can form pharmaceutically acceptable salts with various amino acids, in addition to the acids

5 mentioned above. Compounds of the invention that are acidic in nature are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include alkali metal or alkaline earth metal salts and, particularly, calcium, magnesium, sodium lithium, zinc, potassium, and iron salts.

As used herein, the term "solvate" means a compound of the invention or a salt
10 thereof, that further includes a stoichiometric or non-stoichiometric amount of a solvent bound by non-covalent intermolecular forces. Preferred solvents are volatile, non-toxic, and/or acceptable for administration to humans in trace amounts.

As used herein, the term "hydrate" means a compound of the invention or a salt
15 thereof, that further includes a stoichiometric or non-stoichiometric amount of water bound by non-covalent intermolecular forces.

The term "clathrate" means a compound of the invention or a salt thereof in the form of a crystal lattice that contains spaces (*e.g.*, channels) that have a guest molecule (*e.g.*, a solvent or water) trapped within.

"Altering lipid metabolism" indicates an observable (measurable) change in at least
20 one aspect of lipid metabolism, including but not limited to total blood lipid content, blood HDL cholesterol, blood LDL cholesterol, blood VLDL cholesterol, blood triglyceride, blood Lp(a), blood apo A-I, blood apo E and blood non-esterified fatty acids.

"Altering glucose metabolism" indicates an observable (measurable) change in at least one aspect of glucose metabolism, including but not limited to total blood glucose
25 content, blood insulin, the blood insulin to blood glucose ratio, insulin sensitivity, and oxygen consumption.

As used herein, the term "alkyl group" means a saturated, monovalent, unbranched or branched hydrocarbon chain. Examples of alkyl groups include, but are not limited to, (C₁-C₆)alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl,
30 2-methyl-2-propyl, 2-methyl-1-butyl, 3-methyl-1-butyl, 2-methyl-3-butyl, 2,2-dimethyl-1-propyl, 2-methyl-1-pentyl, 3-methyl-1-pentyl, 4-methyl-1-pentyl, 2-methyl-2-pentyl, 3-methyl-2-pentyl, 4-methyl-2-pentyl, 2,2-dimethyl-1-butyl, 3,3-dimethyl-1-butyl, 2-ethyl-1-butyl, butyl, isobutyl, *t*-butyl, pentyl, isopentyl, neopentyl, and hexyl, and longer alkyl

groups, such as heptyl, and octyl. An alkyl group can be unsubstituted or substituted with one or two suitable substituents.

An “alkenyl group” means a monovalent, unbranched or branched hydrocarbon chain having one or more double bonds therein. The double bond of an alkenyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkenyl groups include, but are not limited to (C₂-C₆)alkenyl groups, such as vinyl, allyl, butenyl, pentenyl, hexenyl, butadienyl, pentadienyl, hexadienyl, 2-ethylhexenyl, 2-propyl-2-butenyl, 4-(2-methyl-3-butene)-pentenyl. An alkenyl group can be unsubstituted or substituted with one or two suitable substituents.

An “alkynyl group” means monovalent, unbranched or branched hydrocarbon chain having one or more triple bonds therein. The triple bond of an alkynyl group can be unconjugated or conjugated to another unsaturated group. Suitable alkynyl groups include, but are not limited to, (C₂-C₆)alkynyl groups, such as ethynyl, propynyl, butynyl, pentynyl, hexynyl, methylpropynyl, 4-methyl-1-butynyl, 4-propyl-2-pentynyl, and 4-butyl-2-hexynyl. An alkynyl group can be unsubstituted or substituted with one or two suitable substituents.

An “aryl group” means a monocyclic or polycyclic-aromatic radical comprising carbon and hydrogen atoms. Examples of suitable aryl groups include, but are not limited to, phenyl, tolyl, anthacenyl, fluorenyl, indenyl, azulenyl, and naphthyl, as well as benzo-fused carbocyclic moieties such as 5,6,7,8-tetrahydronaphthyl. An aryl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the aryl group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as “(C₆)aryl”.

A “heteroaryl group” means a monocyclic- or polycyclic aromatic ring comprising carbon atoms, hydrogen atoms, and one or more heteroatoms, preferably 1 to 3 heteroatoms, independently selected from nitrogen, oxygen, and sulfur. Illustrative examples of heteroaryl groups include, but are not limited to, pyridinyl, pyridazinyl, pyrimidyl, pyrazyl, triazinyl, pyrrolyl, pyrazolyl, imidazolyl, (1,2,3,)- and (1,2,4)-triazolyl, pyrazinyl, pyrimidinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, furyl, phienyl, isoxazolyl, and oxazolyl. A heteroaryl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, a heteroaryl group is a monocyclic ring, wherein the ring comprises 2 to 5 carbon atoms and 1 to 3 heteroatoms, referred to herein as “(C₂-C₅)heteroaryl”.

A “cycloalkyl group” means a monocyclic or polycyclic saturated ring comprising carbon and hydrogen atoms and having no carbon-carbon multiple bonds. Examples of

cycloalkyl groups include, but are not limited to, (C₃-C₇)cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl group can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl group is a monocyclic ring or bicyclic ring.

5 A “heterocycloalkyl group” means a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and
10 pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 3 to 6 carbon atoms and from 1 to 3 heteroatoms, referred to herein as (C₁-C₆)heterocycloalkyl.

As used herein a “heterocyclic radical” or “heterocyclic ring” means a
15 heterocycloalkyl group or a heteroaryl group.

The term “alkoxy group” means an -O-alkyl group, wherein alkyl is as defined above. An alkoxy group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the alkyl chain of an alkoxy group is from 1 to 6 carbon atoms in length, referred to herein as “(C₁-C₆)alkoxy”.

20 The term “aryloxy group” means an -O-aryl group, wherein aryl is as defined above. An aryloxy group can be unsubstituted or substituted with one or two suitable substituents. Preferably, the aryl ring of an aryloxy group is a monocyclic ring, wherein the ring comprises 6 carbon atoms, referred to herein as “(C₆)aryloxy”.

The term “benzyl” means -CH₂-phenyl.

25 The term “phenyl” means -C₆H₅. A phenyl group can be unsubstituted or substituted with one or two suitable substituents.

A “hydrocarbyl” group means a monovalent group selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, and (C₂-C₈)alkynyl, optionally substituted with one or two suitable substituents. Preferably, the hydrocarbon chain of a hydrocarbyl group is from 1 to 6 carbon atoms in
30 length, referred to herein as “(C₁-C₆)hydrocarbyl”.

A “carbonyl” group is a divalent group of the formula -C(O)-.

An “alkoxycarbonyl” group means a monovalent group of the formula -C(O)-alkoxy. Preferably, the hydrocarbon chain of an alkoxycarbonyl group is from 1 to 8 carbon atoms in length, referred to herein as a “lower alkoxycarbonyl” group.

A "carbamoyl" group means the radical $-C(O)N(R')_2$, wherein R' is chosen from the group consisting of hydrogen, alkyl, and aryl.

As used herein, "halogen" means fluorine, chlorine, bromine, or iodine.

Correspondingly, the meaning of the terms "halo" and "Hal" encompass fluoro, chloro,

5 bromo, and iodo.

As used herein, a "suitable substituent" means a group that does not nullify the synthetic or pharmaceutical utility of the compounds of the invention or the intermediates useful for preparing them. Examples of suitable substituents include, but are not limited to:

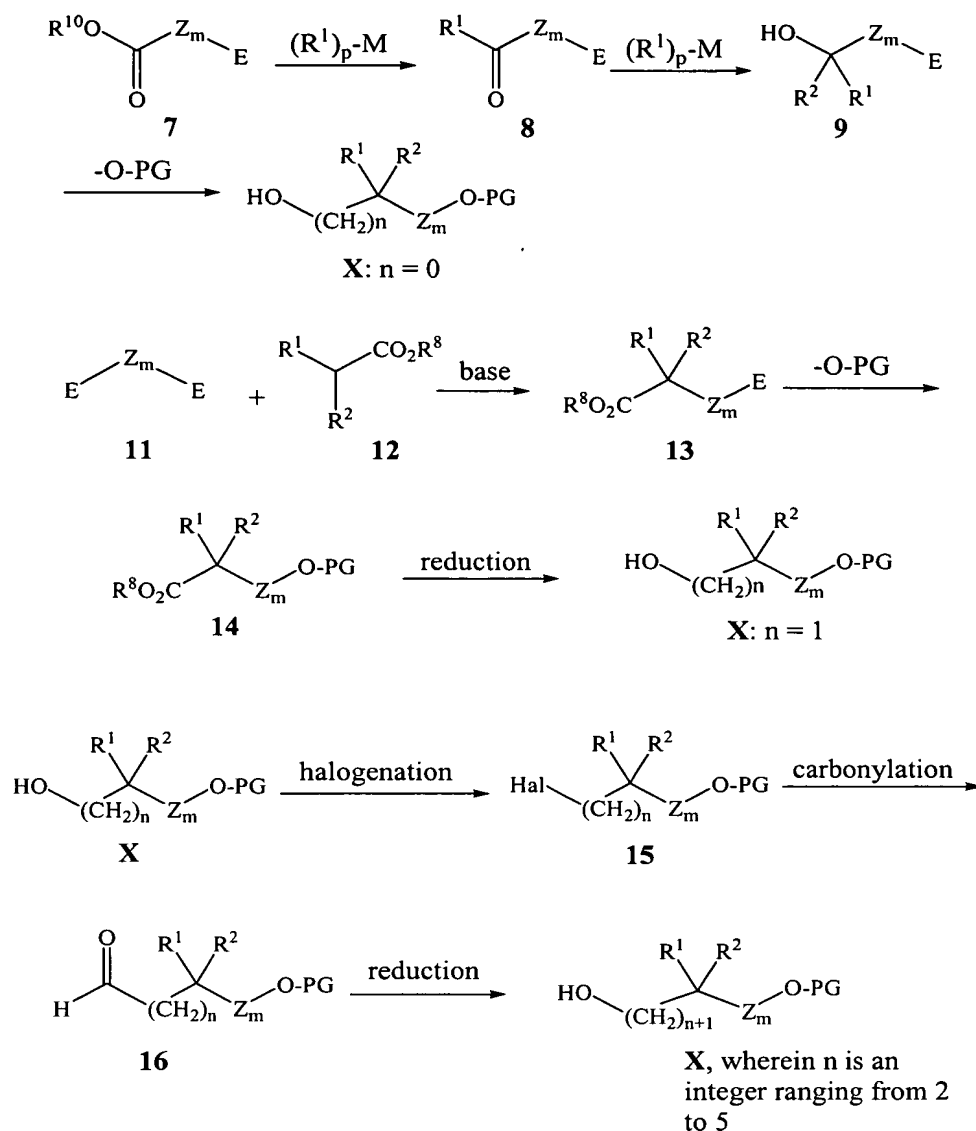
10 (C₁-C₈)alkyl; (C₁-C₈)alkenyl; (C₁-C₈)alkynyl; (C₆)aryl; (C₂-C₅)heteroaryl; (C₃-C₇)cycloalkyl; (C₁-C₈)alkoxy; (C₆)aryloxy; -CN; -OH; oxo; halo, -CO₂H; -NH₂; -NH((C₁-C₈)alkyl); -N((C₁-C₈)alkyl)₂; -NH((C₆)aryl); -N((C₆)aryl)₂; -CHO; -CO((C₁-C₈)alkyl); -CO((C₆)aryl); -CO₂((C₁-C₈)alkyl); and -CO₂((C₆)aryl). One of skill in art can readily choose a suitable substituent based on the stability and pharmacological and synthetic activity of the compound of the invention.

15

4.2 Synthesis of the Compounds of the Invention

The compounds of the invention can be obtained via the synthetic methodology illustrated in Schemes 1-9. Starting materials useful for preparing the compounds of the invention and intermediates thereof, are commercially available or can be prepared from commercially available materials using known synthetic methods and reagents.

Scheme 1: Synthesis of Compounds of Formula 10



Scheme 1 illustrates the synthesis of mono-protected diols of the formula X, wherein n is an integer ranging from 0 to 4 and R¹ and R² are as defined above. Scheme 1 first outlines the synthesis of mono-protected diols X, wherein n is 0, where esters 7 are successively reacted with a first ((R¹)_p-M) then a second ((R²)_p-M) organometallic reagent providing ketones 8 and alcohols 9, respectively. M is a metal and p is the metal's valency value (e.g., the valency of Li is 1 and that of Zn is 2). Suitable metals include, but are not limited to, Zn, Na, Li, and -Mg-Hal, wherein Hal is a halide selected from iodo, bromo, or chloro. Preferably, M is -Mg-Hal, in which case the organometallic reagents, (R¹)_p-Mg-Hal and (R²)_p-Mg-Hal, are known in the art as Grignard reagents. Esters 7 are available commercially (e.g., Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by

well-known synthetic methods, for example, via esterification of the appropriate 5-halovaleric acid (commercially available, *e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin). Both $(R^1)_pM$ and $(R^2)_pM$ are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known methods (see *e.g.*,
5 Kharasch *et al.*, *Grignard Reactions of Non-Metallic Substances*; Prentice-Hall, Englewood Cliffs, NJ, pp. 138-528 (1954) and Hartley; Patai, *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley: New York, pp. 159-306 and pp. 162-175 (1989), both citations are incorporated by reference herein). The reaction of a first $((R^1)_pM)$ then a second $((R^2)_pM)$ organometallic reagent with esters **7** can be performed using the general procedures
10 referenced in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., Wiley: New York, (1992), pp. 920-929 and Eicher, Patai, *The Chemistry of the Carbonyl Group*, pt. 1, pp. 621-693; Wiley: New York, (1966), incorporated by reference herein. For example, the synthetic procedure described in Comins *et al.*, 1981, *Tetrahedron Lett.* 22:1085, incorporated by reference herein, can be used. As one
15 example, the reaction can be performed by adding an organic solution of $(R^1)_pM$ (about 0.5 to about 1 equivalents) to a stirred, cooled (about 0°C to about -80°C) solution comprising esters **7**, under an inert atmosphere (*e.g.*, nitrogen) to give a reaction mixture comprising ketones **8**. Preferably, $(R^1)_pM$ is added at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The
20 progress of the reaction can be followed by using an appropriate analytical method, such as thin-layer chromatography or high-performance-liquid chromatography. Next, an organic solution of $(R^2)_pM$ (about 0.5 to about 1 equivalent) is added to the reaction mixture comprising ketones **8** in the same manner used to add $(R^1)_pM$. After the reaction providing alcohols **9** is substantially complete, the reaction mixture can be quenched and the product
25 can be isolated by workup. Suitable solvents for obtaining alcohols **9** include, but are not limited to, dichloromethane, diethyl ether, tetrahydrofuran, benzene, toluene, xylene, hydrocarbon solvents (*e.g.*, pentane, hexane, and heptane), and mixtures thereof. Preferably, the organic solvent is diethyl ether or tetrahydrofuran. Next, alcohols **9** are converted to mono-protected diols **X**, wherein *n* is 0, using the well-known Williamson
30 ether synthesis. This involves reacting alcohols **9** with -O-PG, wherein -PG is a hydroxy-protecting group. For a general discussion of the Williamson ether synthesis, see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 386-387, and for a list of procedures and reagents useful in the Williamson ether synthesis see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 446-448,

both of which references are incorporated herein by reference. As used herein, a “hydroxy-protecting group” means a group that is reversibly attached to a hydroxy moiety that renders the hydroxy moiety unreactive during a subsequent reaction(s) and that can be selectively cleaved to regenerate the hydroxy moiety once its protecting purpose has been served.

5 Examples of hydroxy-protecting groups are found in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), incorporated herein by reference.

Preferably, the hydroxy-protecting group is stable in a basic reaction medium, but can be cleaved by acid. Examples of suitable base-stable acid-labile hydroxy-protecting groups suitable for use with the invention include, but are not limited to, ethers, such as methyl,

10 methoxy methyl, methylthiomethyl, methoxyethoxymethyl, *bis*(2-chloroethoxy)methyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranlyl, tetrahydrothiofuranlyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, *t*-butyl, allyl, benzyl, *o*-nitrobenzyl, triphenylmethyl, α -naphthylmethyl, *p*-methoxyphenyldiphenylmethyl, 9-(9-phenyl-10-oxo)anthranyl, trimethylsilyl, isopropyldimethylsilyl, *t*-butyldimethylsilyl, *t*-

15 butyldiphenylsilyl, tribenzylsilyl, and triisopropylsilyl; and esters, such as pivaloate, adamantoate, and 2,4,6-trimethylbenzoate. Ethers are preferred, particularly straight chain ethers, such as methyl ether, methoxymethyl ether, methylthiomethyl ether, methoxyethoxymethyl ether, *bis*(2-chloroethoxy)methyl ether. Preferably –PG is methoxymethyl (CH₃OCH₂–). Reaction of alcohols **9** with –O–PG under the conditions of

20 the Williamson ether synthesis require the protection of the hydroxy group. Alcohols **9** are protected with a base-labile protecting group, but stable in the presence of nucleophiles or NaH, Na or other metals used in the next step. Protecting groups recommended for this step are: pivalate, 2,4,6-trimethylbenzoate (mesitoate), alkylmethyl carbonate, or other similar reagents described in Greene, T.W., *Protective Groups in Organic Chemistry*, p.

25 170-187. In a typical experiment, the alcohol **9** is treated with an acid chloride or an anhydride in the presence of a suitable base preferably pyridine or dimethylamino-pyridine in a temperature range of -20°C to 100°C, preferably at 0 °C, for various periods of time, from a few hours to a few days. The reaction may occur with or without the presence of a solvent, with the base catalyst acting as one, or if a solvent is required dichloromethane,

30 tetrachloroethylene, and toluene are preferred. The alcohol **9** is then subjected to the Williamson ether synthesis, which involves adding a base to a stirred organic solution comprising HO–PG (*e.g.*, methoxymethanol), maintained at a constant temperature within the range of about 0°C to about 80°C, preferably at about room temperature. Preferably, the base is added at a rate such that the reaction-mixture temperature remains within about one

to two degrees of the initial reaction-mixture temperature. The base can be added as an organic solution or in undiluted form. Preferably, the base will have a base strength sufficient to deprotonate a proton, wherein the proton has a pK_a of greater than about 15, preferably greater than about 20. As is well known in the art, the pK_a is a measure of the acidity of an acid H-A, according to the equation $pK_a = -\log K_a$, wherein K_a is the equilibrium constant for the proton transfer. The acidity of an acid H-A is proportional to the stability of its conjugate base -A. For tables listing pK_a values for various organic acids and a discussion on pK_a measurement, see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 248-272, incorporated herein by reference. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride. The preferred base is sodium hydride. Solvents suitable for reacting alcohols **9** with -OPG include, but are not limited, to dimethyl sulfoxide, dichloromethane, ethers, and mixtures thereof, preferably tetrahydrofuran. After addition of the base, the reaction mixture can be adjusted to within a temperature range of about 0°C to about room temperature and alcohols **9** can be added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. Alcohols **9** can be diluted in an organic solvent or added in their undiluted form. The resulting reaction mixture is stirred until the reaction is substantially complete as determined by using an appropriate analytical method, preferably by gas chromatography, then the mono-protected alcohols **X** can be isolated by workup and purification. Mono-protected alcohols **X** are further treated with a suitable base or nucleophile to remove the OPG protecting group. The preferred reagent for this purpose is lithium aluminum hydride, using as solvent THF, diethyl ether, diisopropyl ether, *t*-butyl-methyl ether or mixtures of solvents, at temperatures ranging from -20°C to 50°C and reaction times from 1 hour to 24 hours. Such Procedures are extensively described in Greene, T. W., *Protective Groups in Organic Chemistry*, p.170-187. The workup of the resulting reaction mixture is performed when the deprotection is complete, which is determined by using the appropriate analytical method, such as thin-layer chromatography or HPLC. Alcohols **X** are isolated from the reaction mixture by methods well-known in the art.

Next, Scheme 1 outlines a method useful for synthesizing mono-protected diols **X**, wherein *n* is 1. First, compounds **11**, wherein E is a suitable leaving group, are reacted with compounds **12**, wherein R¹ and R² are as defined above and R⁸ is H, (C₁-C₆)alkyl or (C₆)aryl, providing compounds **13**. Suitable leaving groups are well known in the art, for example, but not limited to halides, such as chloride, bromide, and iodide; aryl- or alkylsulfonyloxy, substituted arylsulfonyloxy (e.g., tosyloxy or mesyloxy); substituted alkylsulfonyloxy (e.g., haloalkylsulfonyloxy); phenoxy or substituted phenoxy; and acyloxy groups. Compounds **11** are available commercially (e.g., Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known methods such as halogenation or sulfonation of butanediol. Compounds **12** are also available commercially (e.g., Aldrich Chemical Co., Milwaukee, Wisconsin) or by well-known methods, such as those listed in Larock *Comprehensive Organic Transformations*; Wiley-VCH: New York, 1999, pp. 1754-1755 and 1765. A review on alkylation of esters of type **12** is given in J. Mulzer in *Comprehensive Organic Functional Transformations*, Pergamon, Oxford 1995, pp. 148-151 and exemplary synthetic procedures for reacting compounds **11** with compounds **12** are described in United States Patent No. 5,648,387, column 6 and Ackerly, *et al.*, 1995, *J. Med. Chem.* **1608**, all of which citations are incorporated by reference herein. The reaction requires the presence of a suitable base. Preferably, a suitable base will have a pK_a of greater than about 25, more preferably greater than about 30. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; hydride bases such as sodium hydride and potassium hydride. Metal amide bases, such as lithium diisopropylamide are preferred. Preferably, to react compounds **11** with compounds **12**, a solution of about 1 to about 1.2 equivalents of a suitable base is added to a stirred solution comprising esters **12** and a suitable organic solvent, under an inert atmosphere, the solution maintained at a constant temperature within the range of about -95 °C to about room temperature, preferably at about -78 °C to about -20°C. Preferably, the base is diluted in a suitable organic solvent before addition. Preferably, the base is added at a rate of about 1.5 moles per hour. Organic solvents suitable for the reaction of compounds **11** with the compounds **12** include, but are not limited to, diethyl ether, tetrahydrofuran, benzene, toluene, xylene, hydrocarbon solvents (e.g., pentane, hexane, and heptane), and mixtures thereof. After

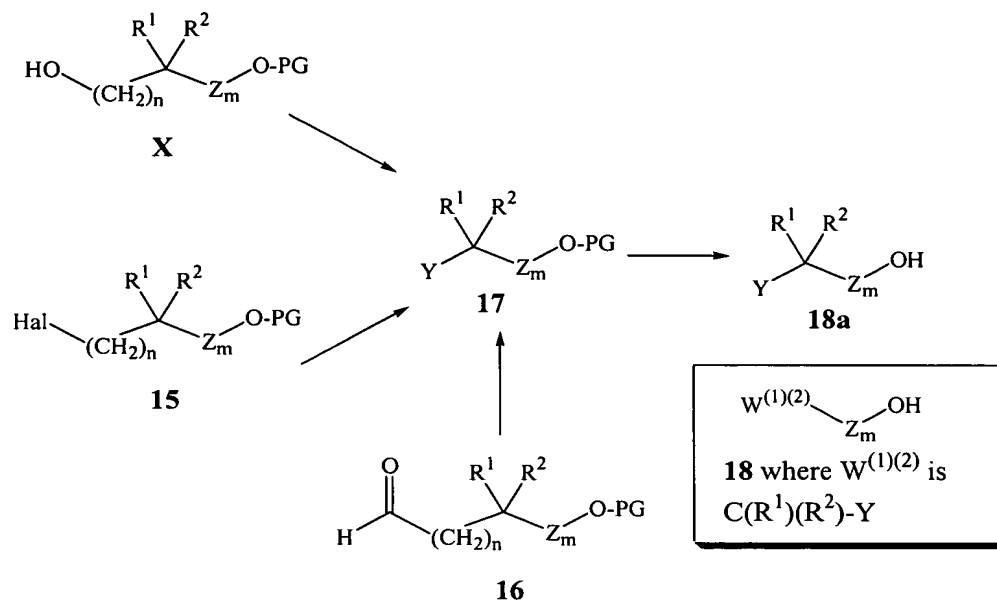
addition of the base, the reaction mixture is allowed to stir for about 1 to about 4 hours, and a compound 11, preferably dissolved in a suitable organic solvent, is added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. After addition of compounds 11, the reaction-mixture temperature can be adjusted to within a temperature range of about -20 °C to about room temperature, preferably to about room temperature, and the reaction mixture is allowed to stir until the reaction is substantially complete as determined by using an appropriated analytical method, preferably thin-layer chromatography or high-performance liquid chromatography. Then the reaction mixture is quenched and compounds 13, wherein n is 1 can be isolated by workup. Compounds 14 are then synthesized by reacting compounds 13 with -O-PG according to the protocol described above for reacting alcohols 9 with -O-PG. Next, compounds 14 can be converted to mono-protected diols X, wherein n is 1, by reduction of the ester group of compounds 14 to an alcohol group with a suitable reducing agent. A wide variety of reagents are available for reduction of such esters to alcohols, *e.g.*, see M. Hudlicky, *Reductions in Organic Chemistry*, 2nd ed., 1996 pp. 212-217, incorporated by reference herein. Preferably, the reduction is effected with a hydride type reducing agent, for example, lithium aluminum hydride, lithium borohydride, lithium triethyl borohydride, diisobutylaluminum hydride, lithium trimethoxyaluminum hydride, or sodium *bis*(2-methoxy)aluminum hydride. For exemplary procedures for reducing esters to alcohols, see Nystrom *et al.*, 1947, *J. Am. Chem. Soc.* 69:1197; and Moffet *et al.*, 1963, *Org. Synth., Collect.* 834(4), lithium aluminum hydride; Brown *et al.*, 1965, *J. Am. Chem. Soc.* 87:5614, lithium trimethoxyaluminum hydride; Cerny *et al.*, 1969, *Collect. Czech. Chem. Commun.* 34:1025, sodium *bis*(2-methoxy)aluminum hydride; Nystrom *et al.*, 1949, *J. Am. Chem.* 71:245, lithium borohydride; and Brown *et al.*, 1980, *J. Org. Chem.* 45:1, lithium triethyl borohydride, all of which citations are incorporated herein by reference. Preferably, the reduction is conducted by adding an organic solution of compounds 14 to a stirred mixture comprising a reducing agent, preferably lithium aluminum hydride, and an organic solvent. During the addition, the reaction mixture is maintained at a constant temperature within the range of about -20 °C to about 80 °C, preferably at about room temperature. Organic solvents suitable for reacting 13 with -OPG include, but are not limited to, dichloromethane, diethyl ether, tetrahydrofuran or mixtures thereof, preferably tetrahydrofuran. After the addition, the reaction mixture is stirred at a constant temperature within the range of about room temperature to about 60°C, until the reaction is substantially complete as determined by using an appropriate analytical method, preferably thin-layer

chromatography or high-performance-liquid chromatography. Then the reaction mixture can be quenched and mono-protected diols **X**, wherein n is 1, can be isolated by workup and purification.

Scheme 1 next illustrates a three step synthetic sequence for homologating mono-protected diols **X** comprising: (a) halogenation (converting $-\text{CH}_2\text{OH}$ to $-\text{CH}_2\text{-Hal}$); (b) carbonylation (replacing $-\text{Hal}$ with $-\text{CHO}$); and (c) reduction (converting $-\text{CHO}$ to $-\text{CH}_2\text{OH}$), wherein a reaction sequence of (a), (b), and (c) increases the value of n by 1. In step (a) protected halo-alcohols **15**, wherein Hal is a halide selected from the group of chloro, bromo, or iodo, preferably iodo, can be prepared by halogenating mono-protected diols **X**, by using well-known methods (for a discussion of various methods for conversion of alcohols to halides see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 431-433, incorporated herein by reference). For example, protected iodo-alcohols **15** can be synthesized starting from mono-protected diols **X** by treatment with $\text{Ph}_3\text{I}/\text{imidazole}$ (Garegg *et al.*, 1980, *J.C.S Perkin I* 2866); 1,2-diphenylene phosphorochloridite/ I_2 (Corey *et al.*, 1967, *J. Org. Chem.* 82:4160); or preferably with $\text{Me}_3\text{SiCl}/\text{NaI}$ (Olah *et al.*, 1979, *J. Org. Chem.* 44:8, 1247), all of which citations are incorporated by reference herein. Step (b); carbonylation of alkyl halides, such as protected halo-alcohols **15**, is reviewed in Olah *et al.*, 1987, *Chem Rev.* 87:4, 671; and March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 483-484, both of which are incorporated by reference herein. Protected halo-alcohols **15** can be carbonylated with $\text{Li}(\text{BF}_3\cdot\text{Et}_2\text{O})/\text{HCONMe}_2$ using the procedure described in Maddaford *et al.*, 1993, *J. Org. Chem.* 58:4132; Becker *et al.*, 1982, *J. Org. Chem.* 32:97; or Myers *et al.*, 1992, *J. Am. Chem. Soc.* 114:9369 or, alternatively, with an organometallic/*N*-formylmorpholine using the procedure described in Olah *et al.*, 1984, *J. Org. Chem.* 49:3856 or Vogtle *et al.*, 1987, *J. Org. Chem.* 52:5560, all of which citations are incorporated by reference herein. The method described in Olah *et al.*, 1984, *J. Org. Chem.* 49:3856 is preferred. Reduction step (c) useful for synthesizing mono-protected diols **X** from aldehydes **16**, can be accomplished by well-known methods in the art for reduction of aldehydes to the corresponding alcohols (for a discussion see M. Hudlicky, *Reductions in Organic Chemistry*, 2nd ed., 1996 pp 137-139), for example, by catalytic hydrogenation (see e.g., Carothers, 1949, *J. Am. Chem. Soc.* 46:1675) or, preferably by reacting aldehydes **16** with a hydride reducing agent, such as lithium aluminum hydride, lithium borohydride, sodium borohydride (see e.g., the procedures described in Chaikin *et al.*, 1949, *J. Am. Chem. Soc.* 71:3245; Nystrom *et al.*, 1947, *J. Am. Chem. Soc.* 69:1197; and Nystrom *et al.*, 1949, *J.*

Am. Chem. 71:3245, all of which are incorporated by reference herein). Reduction with lithium aluminum hydride is preferred.

Scheme 2: Synthesis of Compounds of Formula 18a, which correspond to Compounds $W^{(1)(2)}-Z_m-OH$, Wherein $W^{(1)(2)}$ is $C(R^1)(R^2)-Y$



5

Scheme 2 outlines methodology for the synthesis of protected alcohols **18a** wherein Y, R^1 , R^2 , Z, and m are defined as above. Protected alcohols **18a** correspond to compounds of the formula $W^{(1)(2)}-Z_m-OPG$, wherein $W^{(1)(2)}$ is $C(R^1)(R^2)-Y$.

Protected alcohols **17**, wherein Y comprises a $-C(O)OH$ group, can be synthesized by oxidizing mono-protected diols **X** with an agent suitable for oxidizing a primary alcohol to a carboxylic acid (for a discussion see M. Hudlicky, *Oxidations in Organic Chemistry*, ACS Monograph 186, 1990, pp. 127-130, incorporated by reference herein). Suitable oxidizing agents include, but are not limited to, pyridinium dichromate (Corey *et al.*, 1979, *Tetrahedron Lett.* 399); manganese dioxide (Ahrens *et al.*, 1967, *J. Heterocycl. Chem.* 4:625); sodium permanganate monohydrate (Menger *et al.*, 1981, *Tetrahedron Lett.* 22:1655); and potassium permanganate (Sam *et al.*, 1972, *J. Am. Chem. Soc.* 94:4024), all of which citations are incorporated by reference herein. The preferred oxidizing reagent is pyridinium dichromate. In an alternative synthetic procedure, protected alcohols **17**, wherein Y comprises a $-C(O)OH$ group, can be synthesized by treatment of protected halo-alcohols **15**, wherein X is iodo, with CO or CO₂, as described in Bailey *et al.*, 1990, *J. Org. Chem.* 55:5404 and Yanagisawa *et al.*, 1994, *J. Am. Chem. Soc.* 116:6130, the two of which citations are incorporated by reference herein. Protected alcohols **17**, wherein Y comprises $-C(O)OR^5$, wherein R^5 is as defined above, can be synthesized by oxidation of mono-

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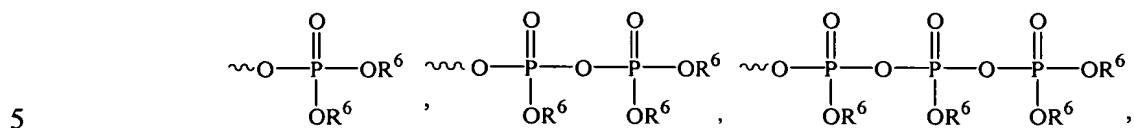
protected diols **X** in the presence of R^5OH (see generally, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1196). An exemplary procedure for such an oxidation is described in Stevens *et al.*, 1982, *Tetrahedron Lett.* 23:4647 (HOCl); Sundararaman *et al.*, 1978, *Tetrahedron Lett.* 1627 (O_3/KOH); Wilson *et al.*, 1982, *J. Org. Chem.* 47:1360 ($t\text{-BuOOH}/Et_3N$); and Williams *et al.*, 1988, *Tetrahedron Lett.* 29:5087 (Br_2), the four of which citations are incorporated by reference herein.

Preferably, protected alcohols **17**, wherein Y comprises a $-C(O)OR^5$ group are synthesized from the corresponding carboxylic acid (*i.e.*, **17**, wherein Y comprises $-C(O)OH$) by esterification with R^5OH (*e.g.*, see March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 393-394, incorporated by reference herein). In another alternative synthesis, protected alcohols **17**, wherein Y comprises $-C(O)OR^5$, can be prepared from protected halo-alcohols **15** by carbonylation with transition metal complexes (*see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 484-486; Urata *et al.*, 1991, *Tetrahedron Lett.* 32:36, 4733); and Ogata *et al.*, 1969, *J. Org. Chem.* 39:85, the three of which citations are incorporated by reference herein).

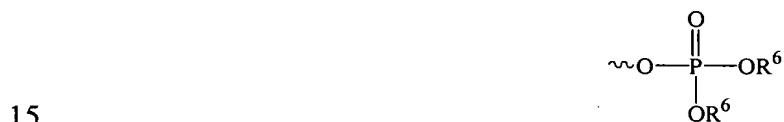
Protected alcohols **17**, wherein Y comprises $-OC(O)R^5$, wherein R^5 is as defined above, can be prepared by acylation of mono-protected diols **X** with a carboxylate equivalent such as an acyl halide (*i.e.*, $R^5C(O)\text{-Hal}$, wherein Hal is iodo, bromo, or chloro, *see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392 and *Org. Synth. Coll. Vol. III*, Wiley, NY, pp. 142, 144, 167, and 187 (1955)) or an anhydride (*i.e.*, $R^5C(O)\text{-O-(O)CR}^5$, *see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392-393 and *Org. Synth. Coll. Vol. III*, Wiley, NY, pp. 11, 127, 141, 169, 237, 281, 428, 432, 690, and 833 (1955), all of which citations are incorporated herein by reference). Preferably, the reaction is conducted by adding a base to a solution comprising mono-protected diols **X**, a carboxylate equivalent, and an organic solvent, which solution is preferably maintained at a constant temperature within the range of 0°C to about room temperature. Solvents suitable for reacting mono-protected diols **X** with a carboxylate equivalent include, but are not limited to, dichloromethane, toluene, and ether, preferably dichloromethane. Suitable bases include, but are not limited to, hydroxide sources, such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate; or an amine such as triethylamine, pyridine, or dimethylaminopyridine. The progress of the reaction can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance

liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols 17, wherein Y comprises one of the following phosphate ester groups



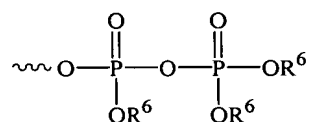
wherein R⁶ is defined as above, can be prepared by phosphorylation of mono-protected diols X according to well-known methods (for a general reviews, see Corbridge *Phosphorus: An Outline of its Chemistry, Biochemistry, and Uses*, Studies in Inorganic Chemistry, 3rd ed., pp. 357-395 (1985); Ramirez *et al.*, 1978, *Acc. Chem. Res.* **11**:239; and
 10 Kalckare *Biological Phosphorylations*, Prentice-Hall, New York (1969); J. B. Sweeny in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 2, pp. 104-109, the four of which are incorporated herein by reference). Protected alcohols 17 wherein Y comprises a monophosphate group of the formula:



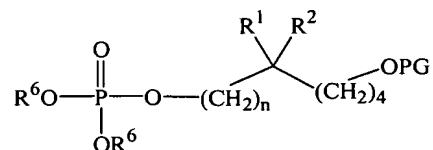
wherein R⁶ is defined as above, can be prepared by treatment of mono-protected diol X with phosphorous oxychloride in a suitable solvent, such as xylene or toluene, at a constant temperature within the range of about 100°C to about 150°C for about 2 hours to about 24 hours. After the reaction is deemed substantially complete, by using an appropriate
 20 analytical method, the reaction mixture is hydrolyzed with R⁶-OH. Suitable procedures are referenced in Houben-Weyl, *Methoden der Organische Chemie*, Georg Thieme Verlag Stuttgart 1964, vol. 12/2, pp. 143-210 and 872-879, incorporated by reference herein. Alternatively, when both R⁶ are hydrogen, can be synthesized by reacting mono-protected diols X with silyl polyphosphate (Okamoto *et al.*, 1985, *Bull Chem. Soc. Jpn.* **58**:3393,
 25 incorporated herein by reference) or by hydrogenolysis of their benzyl or phenyl esters (Chen *et al.*, 1998, *J. Org. Chem.* **63**:6511, incorporated herein by reference). In another alternative procedure, when R⁶ is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl, the monophosphate esters can be prepared by reacting mono-protected diols X with appropriately substituted phosphoramidites followed by oxidation of the intermediate with
 30 *m*-chloroperbenzoic acid (Yu *et al.*, 1988, *Tetrahedron Lett.* **29**:979, incorporated herein by

reference) or by reacting mono-protected diols **X** with dialkyl or diaryl substituted phosphorochloridates (Pop, *et al*, 1997, *Org. Prep. and Proc. Int.* 29:341, incorporated herein by reference). The phosphoramidites are commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or readily prepared according to literature procedures (see *e.g.*, Uhlmann *et al*, 1986, *Tetrahedron Lett.* 27:1023 and Tanaka *et al.*, 1988, *Tetrahedron Lett.* 29:199, both of which are incorporated herein by reference). The phosphorochloridates are also commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared according to literature methods (*e.g.*, Gajda *et al*, 1995, *Synthesis* 25:4099. In still another alternative synthesis, protected alcohols **17**, wherein Y comprises a monophosphate group and R⁶ is alkyl or aryl, can be prepared by reacting IP⁺(OR⁶)₃ with mono-protected diols **X** according to the procedure described in Stowell *et al.*, 1995, *Tetrahedron Lett.* 36:11, 1825 or by alkylation of protected halo alcohols **15** with the appropriate dialkyl or diaryl phosphates (see *e.g.*, Okamoto, 1985, *Bull Chem. Soc. Jpn.* 58:3393, incorporated herein by reference).

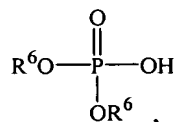
Protected alcohols **17** wherein Y comprises a diphosphate group of the formula



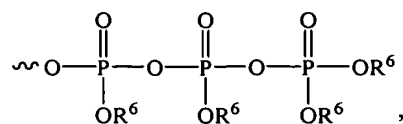
wherein R⁶ is defined as above, can be synthesized by reacting the above-discussed monophosphates of the formula:



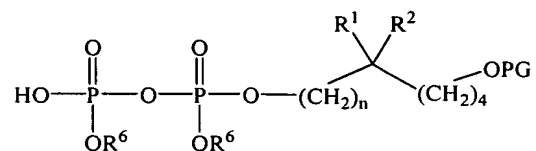
with a phosphate of the formula



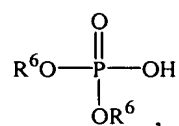
(commercially available, *e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of carbodiimide such as dicyclohexylcarbodiimide, as described in Houben-Weyl, *Methoden der Organische Chemie*, Georg Thieme Verlag Stuttgart 1964, vol. 12/2, pp. 881-885. In the same fashion, protected alcohols **17**, wherein Y comprises a triphosphate group of the formula:



can be synthesized by reacting the above-discussed diphosphate protected alcohols, of the formula:

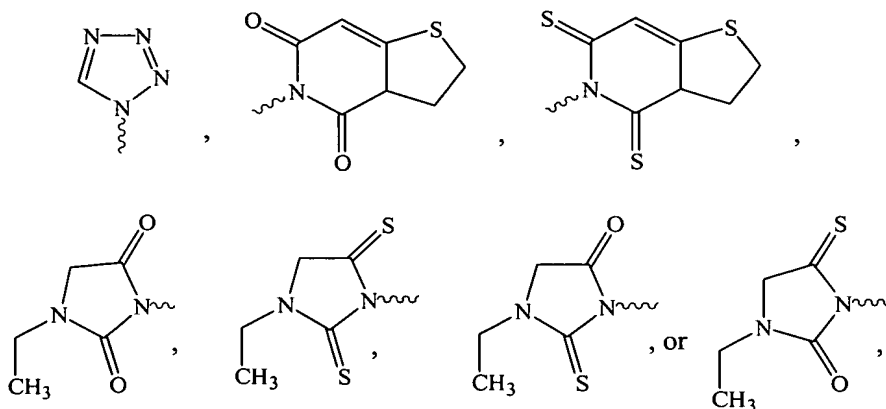


5 with a phosphate of the formula:



as described above. Alternatively, when R^6 is H, protected alcohols **17** wherein Y comprises the triphosphate group, can be prepared by reacting mono-protected diols **X** with salicyl phosphorochloridite and then pyrophosphate and subsequent cleavage of the adduct thus obtained with iodine in pyridine as described in Ludwig *et al.*, 1989, *J. Org. Chem.* 54:631, incorporated herein by reference.

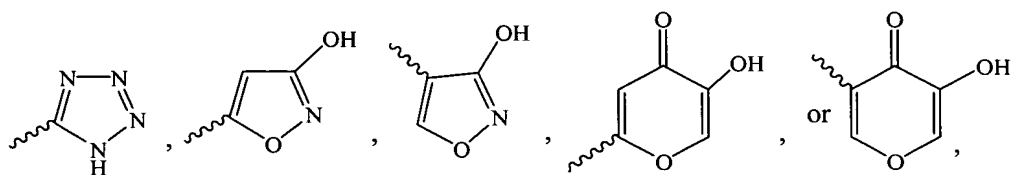
Protected alcohols **17**, wherein Y is $-\text{SO}_3\text{H}$ or a heterocyclic group selected from the group consisting of:



15 can be prepared by halide displacement from protected halo-alcohols **15**. Thus, when Y is $-\text{SO}_3\text{H}$, protected alcohols **17** can be synthesized by reacting protected halo-alcohols **15** with sodium sulfite as described in Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 1965, pp. 136-148 and pp. 161-163; *Org. Synth. Coll.* Vol. II, Wiley, NY, 558, 564 (1943); and *Org. Synth. Coll.* Vol. IV, Wiley, NY, 529 (1963), all three of which are incorporated

herein by reference. When Y is one of the above-mentioned heterocycles, protected alcohols **17** can be prepared by reacting protected halo-alcohols **15** with the corresponding heterocycle in the presence of a base. The heterocycles are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared by well-known synthetic methods (see the procedures described in Ware, 1950, *Chem. Rev.* **46**:403-470, incorporated herein by reference). Preferably, the reaction is conducted by stirring a mixture comprising **15**, the heterocycle, and a solvent at a constant temperature within the range of about room temperature to about 100°C, preferably within the range of about 50°C to about 70°C for about 10 to about 48 hours. Suitable bases include hydroxide bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate. Preferably, the solvent used in forming protected alcohols **17** is selected from dimethylformamide; formamide; dimethyl sulfoxide; alcohols, such as methanol or ethanol; and mixtures thereof. The progress of the reaction can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols **17**, wherein Y is a heteroaryl ring selected from



can be prepared by metallating the suitable heteroaryl ring then reacting the resulting metallated heteroaryl ring with protected halo-alcohols **15** (for a review, see Katritzky *Handbook of Heterocyclic Chemistry*, Pergamon Press: Oxford 1985). The heteroaryl rings are available commercially or prepared by well-known synthetic methods (*see e.g.*, Joule *et al.*, *Heterocyclic Chemistry*, 3rd ed., 1995; De Sarlo *et al.*, 1971, *J. Chem. Soc. (C)* **86**; Oster *et al.*, 1983, *J. Org. Chem.* **48**:4307; Iwai *et al.*, 1966, *Chem. Pharm. Bull.* **14**:1277; and United States Patent No. 3,152,148, all of which citations are incorporated herein by reference). As used herein, the term “metallating” means the forming of a carbon-metal bond, which bond may be substantially ionic in character. Metallation can be accomplished by adding about 2 equivalents of strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the heterocycle. Two equivalents of base are required: one equivalent of the base deprotonates the –OH group or the –NH group, and the second equivalent metallates the heteroaryl ring. Alternatively, the hydroxy group of the heteroaryl

ring can be protected with a base-stable, acid-labile protecting group as described in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), incorporated herein by reference. Where the hydroxy group is protected, only one equivalent of base is required. Examples of suitable base-stable, acid-labile hydroxyl-protecting groups, include

5 but are not limited to, ethers, such as methyl, methoxy methyl, methylthiomethyl, methoxyethoxymethyl, *bis*(2-chloroethoxy)methyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuran, tetrahydrothiofuran, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, *t*-butyl, allyl, benzyl, *o*-nitrobenzyl, triphenylmethyl, α -naphthylidiphenylmethyl, *p*-methoxyphenyldiphenylmethyl, 9-(9-phenyl-10-oxo)anthranyl,

10 trimethylsilyl, isopropyldimethylsilyl, *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl, tribenzylsilyl, triisopropylsilyl; and esters, such as pivaloate, adamantate, and 2,4,6-trimethylbenzoate. Ethers are preferred, particularly straight chain ethers, such as methyl ether, methoxymethyl ether, methylthiomethyl ether, methoxyethoxymethyl ether, *bis*(2-chloroethoxy)methyl ether. Preferably, the pK_a of the base is higher than the pK_a of the

15 proton of the heterocycle to be deprotonated. For a listing of pK_a s for various heteroaryl rings, see Fraser *et al.*, 1985, *Can. J. Chem.* **63**:3505, incorporated herein by reference. Suitable bases include, but are not limited to, alkylmetal bases such as methyl lithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide,

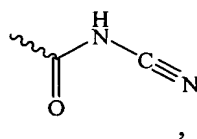
20 lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride. If desired, the organometallic base can be activated with a complexing agent, such as *N,N,N',N'*-tetramethylethylenediamine or hexamethylphosphoramide (1970, *J. Am. Chem. Soc.*

25 **92**:4664, incorporated by reference herein). Solvents suitable for synthesizing protected alcohols **17**, wherein Y is a heteroaryl ring include, but are not limited to, diethyl ether; tetrahydrofuran; and hydrocarbons, such as pentane. Generally, metallation occurs alpha to the heteroatom due to the inductive effect of the heteroatom, however, modification of conditions, such as the identity of the base and solvents, order of reagent addition, reagent

30 addition times, and reaction and addition temperatures can be modified by one of skill in the art to achieve the desired metallation position (*see e.g.*, Joule *et al.*, *Heterocyclic Chemistry*, 3rd ed., 1995, pp. 30-42, incorporated by reference herein) Alternatively, the position of metallation can be controlled by use of a halogenated heteroaryl group, wherein the halogen is located on the position of the heteroaryl ring where metallation is desired (*see e.g.*, Joule

et al., *Heterocyclic Chemistry*, 3rd ed., 1995, p. 33 and Saulnier et al., 1982, *J. Org. Chem.* 47:757, the two of which citations are incorporated by reference herein). Halogenated heteroaryl groups are available commercially (e.g., Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known synthetic methods (see e.g., Joule et al., *Heterocyclic Chemistry*, 3rd ed., 1995, pp. 78, 85, 122, 193, 234, 261, 280, 308, incorporated by reference herein). After metallation, the reaction mixture comprising the metallated heteroaryl ring is adjusted to within a temperature range of about 0°C to about room temperature and protected halo-alcohols **15** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. After addition of protected halo-alcohols **15**, the reaction mixture is stirred at a constant temperature within the range of about room temperature and about the solvent's boiling temperature and the reaction's progress can be monitored by the appropriate analytical technique, preferably thin-layer chromatography or high-performance liquid chromatography. After the reaction is substantially complete, protected alcohols **17** can be isolated by workup and purification. It is to be understood that conditions, such as the identity of protected halo-alcohol **15**, the base, solvents, orders of reagent addition, times, and temperatures, can be modified by one of skill in the art to optimize the yield and selectivity. Exemplary procedures that can be used in such a transformation are described in Shirley et al., 1995, *J. Org. Chem.* 20:225; Chadwick et al., 1979, *J. Chem. Soc., Perkin Trans. 1* 2845; Rewcastle, 1993, *Adv. Het. Chem.* 56:208; Katritzky et al., 1993, *Adv. Het. Chem.* 56:155; and Kessar et al., 1997, *Chem. Rev.* 97:721.

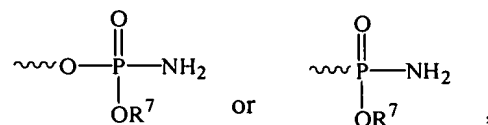
When Y is



protected alcohols **17** can be prepared from their corresponding carboxylic acid derivatives (**17**, wherein Y is –CO₂H) as described in Belletire et al., 1988, *Synthetic Commun.* 18:2063 or from the corresponding acylchlorides (**17**, wherein Y is –CO–halo) as described in Skinner et al., 1995, *J. Am. Chem. Soc.* 77:5440, both citations are incorporated herein by reference. The acylhalides can be prepared from the carboxylic acids by well known procedures such as those described in March, J., *Advanced Organic Chemistry; Reactions*

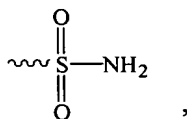
Mechanisms, and Structure, 4th ed., 1992, pp. 437-438, incorporated by reference herein.

When Y is



wherein R⁷ is as defined above, protected alcohols **17** can be prepared by first reacting

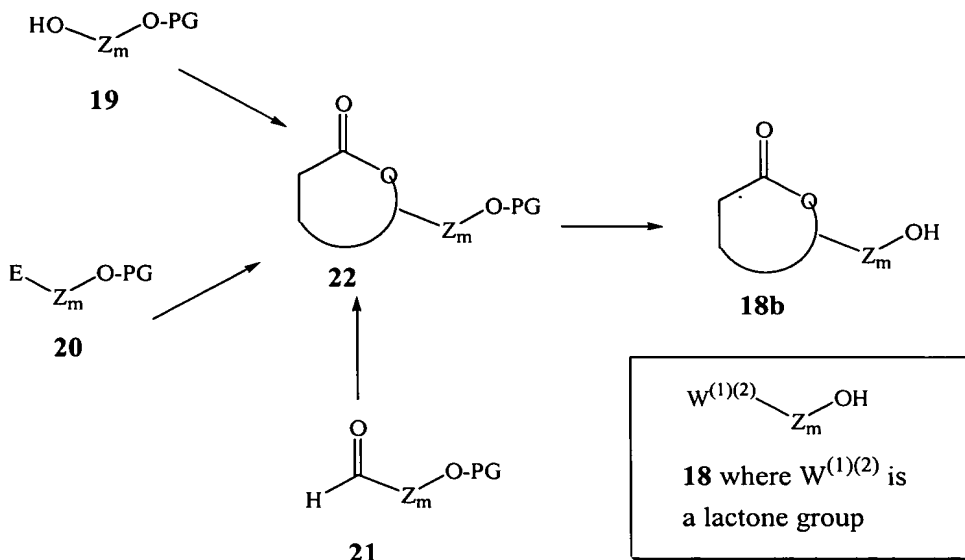
- 5 protected halo-alcohols **15** with a trialkyl phosphite according to the procedure described in Kosolapoff, 1951, *Org. React.* 6:273 followed by reacting the derived phosphonic diester with ammonia according to the procedure described in Smith *et al.*, 1957, *J. Org. Chem.* 22:265, incorporated herein by reference. When Y is



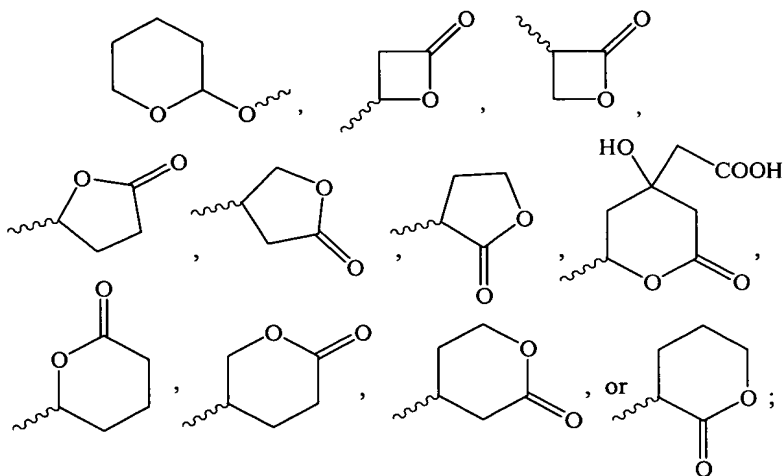
- 10 protected alcohols **17** can be prepared by reacting their sulphonic acid derivatives (*i.e.*, **17**, wherein Y is -SO₃H) with ammonia as described in Sianesi *et al.*, 1971, *Chem. Ber.* 104:1880 and Campagna *et al.*, 1994, *Farmaco, Ed. Sci.* 49:653, both of which citations are incorporated herein by reference).

- As further illustrated in Scheme 2, protected alcohols **17** can be deprotected
- 15 providing alcohols **18a**. The deprotection method depends on the identity of the alcohol-protecting group, *see e.g.*, the procedures listed in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), particularly see pages 48-49, incorporated herein by reference. One of skill in the art will readily be able to choose the appropriate deprotection procedure. When the alcohol is protected as an ether function (*e.g.*,
- 20 methoxymethyl ether), the alcohol is preferably deprotected with aqueous or alcoholic acid. Suitable deprotection reagents include, but are not limited to, aqueous hydrochloric acid, *p*-toluenesulfonic acid in methanol, pyridinium-*p*-toluenesulfonate in ethanol, Amberlyst H-15 in methanol, boric acid in ethylene-glycol-monoethylether, acetic acid in a water-tetrahydrofuran mixture, aqueous hydrochloric acid is preferred. Examples of such
- 25 procedures are described, respectively, in Bernady *et al.*, 1979, *J. Org. Chem.* 44:1438; Miyashita *et al.*, 1977, *J. Org. Chem.* 42:3772; Johnston *et al.*, 1988, *Synthesis* 393; Bongini *et al.*, 1979, *Synthesis* 618; and Hoyer *et al.*, 1986, *Synthesis* 655; Gigg *et al.*, 1967, *J. Chem. Soc. C*, 431; and Corey *et al.*, 1978, *J. Am. Chem. Soc.* 100:1942, all of which are incorporated herein by reference.

correspond to $W^{(1)(2)}-Z_m-OH$, Wherein $W^{(1)(2)}$ is a Lactone Group



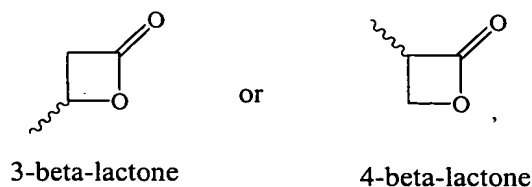
5 **18b.** Compounds **22** and **18b** correspond to compounds of the formula $W^{(1)(2)}\text{-Zm-OPG}$ and $W^{(1)(2)}\text{-Zm-OH}$ respectively, wherein $W^{(1)(2)}$ is a lactone group selected from:



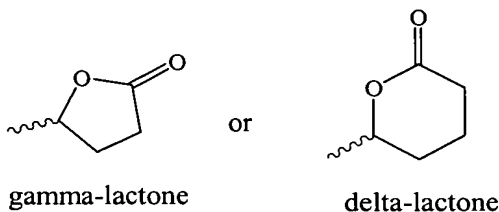
Protected lactone alcohols **22** can be prepared from compounds of the formula **19**, **20**, or **21** by using well-known condensation reactions and variations of the Michael reaction.

10 Methods for the synthesis of lactones are disclosed in Multzer in *Comprehensive Organic*
Functional Group Transformations, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds.
Pergamon: Oxford, 1995, vol 5, pp. 161-173, incorporated herein by reference. Mono-
protected diols **19**, electrophilic protected alcohols **20**, and aldehydes **21** are readily
available either commercially (e.g., Aldrich Chemical Co., Milwaukee, WI) or by well
15 known synthetic procedures.

When $W^{(1)(2)}$ is a beta-lactone group of the formula:



protected lactone alcohols **22** can be prepared from aldehydes **21** and electrophilic protected alcohols **20**, respectively, by a one-pot-addition-lactonization according to the procedure of Masamune *et al.*, 1976, *J. Am. Chem. Soc.* 98:7874 and Danheiser *et al.*, 1991, *J. Org. Chem.* 56:1176, both of which are incorporated herein by reference. This one-pot-addition-lactonization methodology has been reviewed by Multzer in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 5, pp. 161, incorporated herein by reference When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:

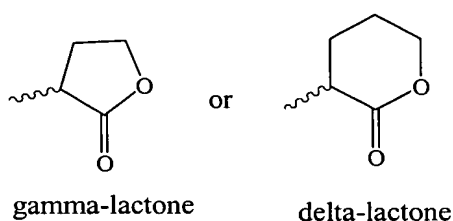


protected lactone alcohols **22** can be prepared from aldehydes **21** according to well known synthetic methodology. For example, the methodology described in Masuyama *et al.*, 2000, *J. Org. Chem.* 65:494; Eisch *et al.*, 1978, *J. Organomet. Chem.* C8 160; Eaton *et al.*, 1947, *J. Org. Chem.* 37:1947; Yunker *et al.*, 1978, *Tetrahedron Lett.* 4651; Bhanot *et al.*, 1977, *J. Org. Chem.* 42:1623; Ehlinger *et al.*, 1980, *J. Am. Chem. Soc.* 102:5004; and Raunio *et al.*, 1957, *J. Org. Chem.* 22:570, all of which citations are incorporated herein by reference. For instance, as described in Masuyama *et al.*, 2000, *J. Org. Chem.* 65:494, aldehydes **21** can be treated with about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, in a suitable organic solvent to give a reaction mixture. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium

hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. The reaction-mixture temperature is adjusted to within the range of about 0°C to about 100°C, preferably about room temperature to about 50°C, and a halide of the formula:

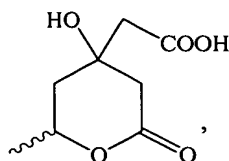


wherein z is 1 or 2 (diluted with a solvent or in undiluted form) is added. The reaction mixture is stirred for a period of about 2 hours to about 48 hours, preferably about 5 to about 10 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **22** can be isolated by workup and purified if desired. When W⁽¹⁾⁽²⁾ is a gamma- or delta-lactone group of the formula:



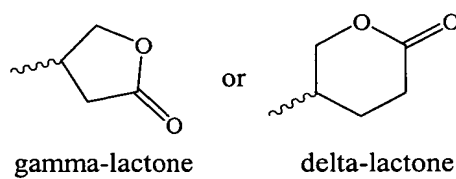
protected lactone alcohols **22** can be synthesized by deprotonating the corresponding lactone with a strong base providing the lactone enolate and reacting the enolate with electrophilic protected alcohols **20** (for a detailed discussion of enolate formation of active methylene compounds such as lactones, see House *Modern Synthetic Reactions*; W. A. Benjamin, Inc. Philippines 1972 pp. 492-570, and for a discussion of reaction of lactone enolates with electrophiles such as carbonyl compounds, see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 944-945, both of which are incorporated herein by reference). Lactone-enolate formation can be accomplished by adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the lactone. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium

diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Solvents suitable for lactone-enolate formation include, but are not limited to, diethyl ether and tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about -78°C to about room temperature, preferably about -50°C to about 0°C , and electrophilic protected alcohols **20** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The reaction mixture is stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **22** can be isolated by workup and purified if desired. When $W^{(1)(2)}$ is a lactone group of the formula:

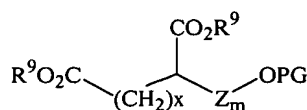


protected lactone alcohols **22** can be prepared from aldehydes **21** according to the procedure described in United States Patent No. 4,622,338, incorporated by reference herein.

When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



protected lactone alcohols **22** can be prepared according to a three step sequence. The first step comprises base-mediated reaction of electrophilic protected alcohols **20** with succinic acid esters (*i.e.*, $R^9O_2CCH_2CH_2CO_2R^9$, wherein R^9 is alkyl) or glutaric acid esters (*i.e.*, $R^9O_2CCH_2CH_2CH_2CO_2R^9$, wherein R^9 is alkyl) providing a diester intermediate of the formula **24**:



24

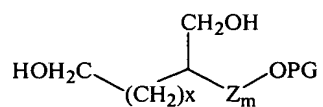
wherein x is 1 or 2 depending on whether the gamma or delta lactone group is desired. The reaction can be performed by adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the succinic or glutaric acid ester.

5 Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and

10 hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about -78°C to about room temperature, preferably about -50°C to about 0°C , and electrophilic protected alcohols **20** (diluted with a solvent or in undiluted form) are

15 added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The reaction mixture is stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed

20 substantially complete, the diester intermediate be isolated by workup and purified if desired. In the second step, the intermediate diester can be reduced, with a hydride reducing agent, to yield a diol of the formula **25**:

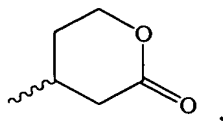


25

25 The reduction can be performed according to the procedures referenced in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1214, incorporated herein by reference). Suitable reducing agents include, but are not limited to, lithium aluminum hydride, diisobutylaluminum hydride, sodium borohydride, and lithium borohydride). In the third step, the diol can be oxidatively cyclized with

30 $\text{RuH}_2(\text{PPh}_3)_4$ to the product protected lactone alcohols **22** according to the procedure of Yoshikawa *et al.*, 1986, *J. Org. Chem.* 51:2034 and Yoshikawa *et al.*, 1983, *Tetrahedron*

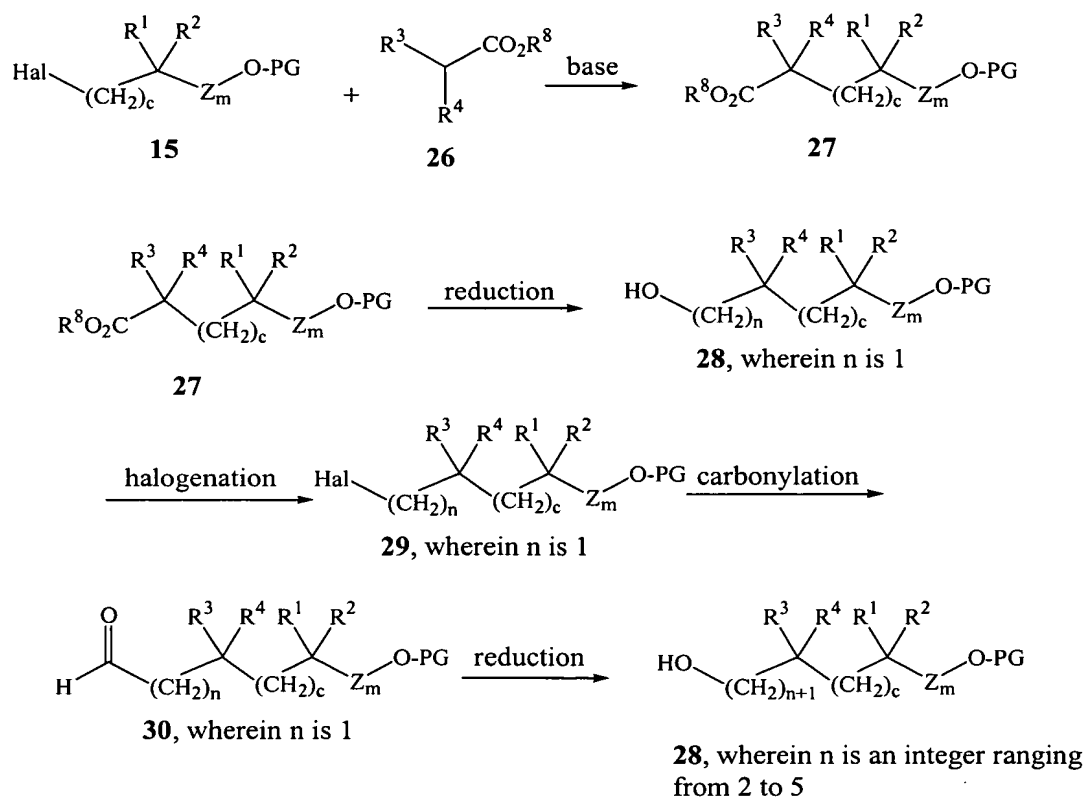
Lett. 26:2677, both of which citations are incorporated herein by reference. When $W^{(1)(2)}$ is a lactone group of the formula:

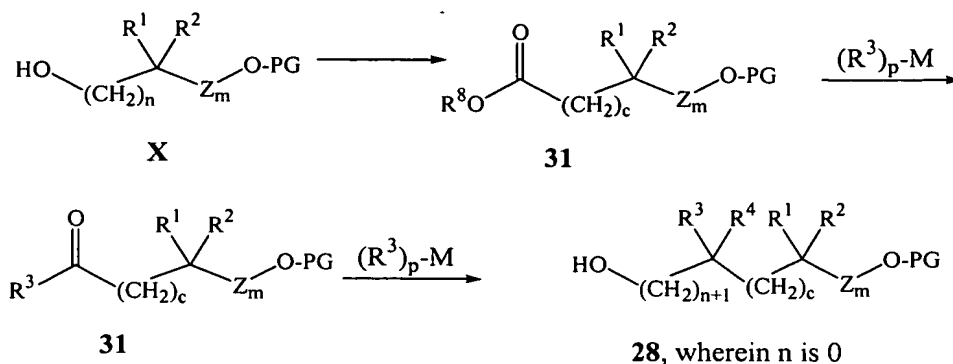


protected lactone alcohols **22** can be synthesized by reacting the Grignard salts of electrophilic protected alcohols **20**, where E is a halide, with 5,6-dihydro-2H-pyran-2-one, commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of catalytic amounts of a 1-dimethylaminoacetyl)pyrrolidine-2-yl)methyl-diarylphosphine-copper (I) iodide complex as described in Tomioka *et al.*, 1995, *Tetrahedron Lett.* 36:4275, incorporated herein by reference.

10

Scheme 4: Synthesis of Compounds of Formula 28

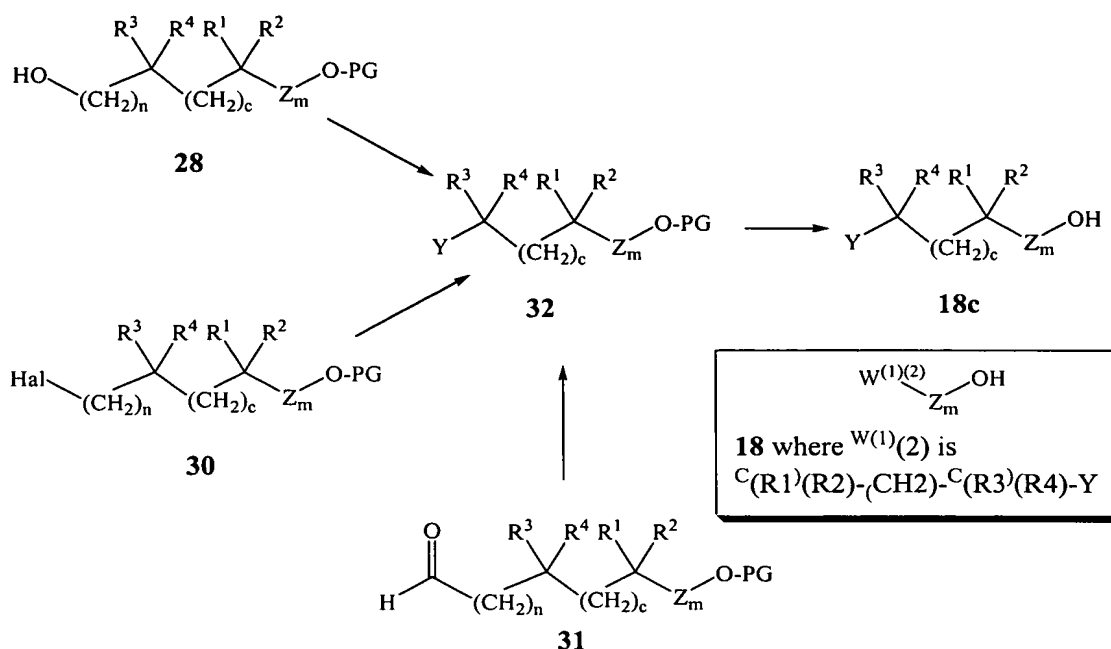




Scheme 4 outlines methodology for the synthesis of protected alcohols **28**. Compounds **28**, wherein n is an integer ranging from 1 to 4 can be prepared from compounds **15** using general synthetic strategy depicted and adapting the synthetic protocols from those discussed for Scheme 1.

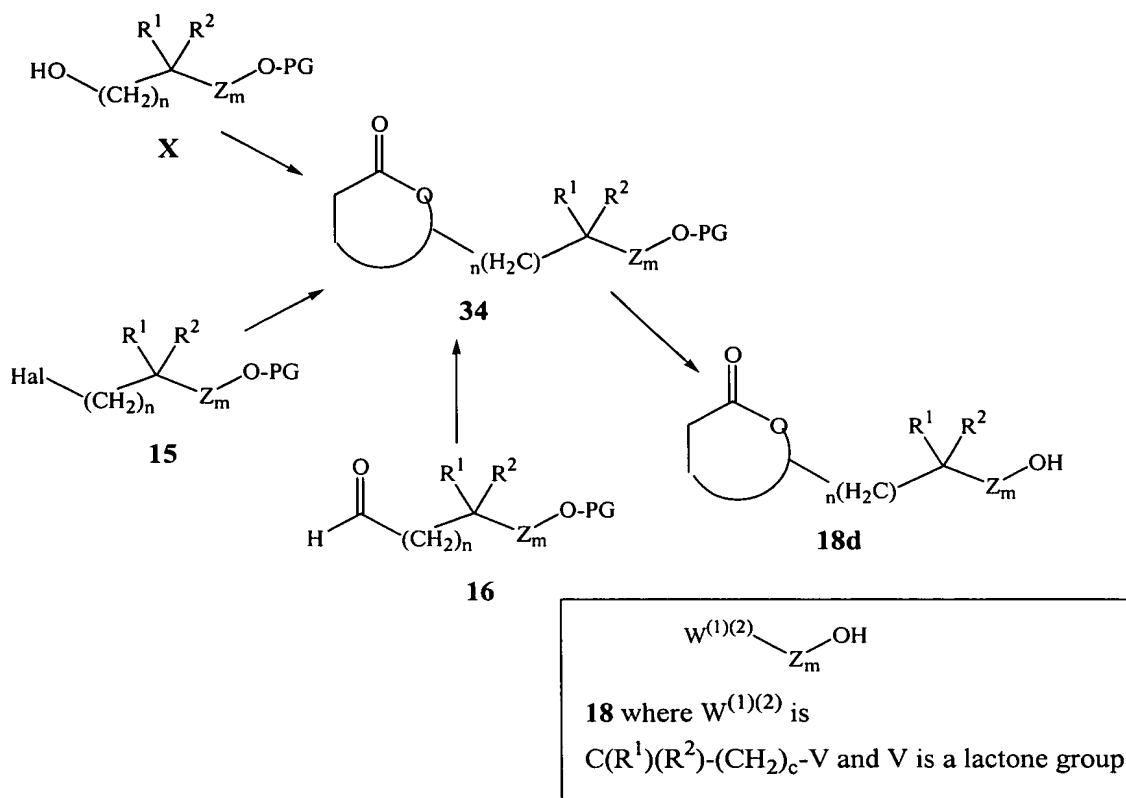
Next, Scheme 4 depicts the general strategy for the synthesis of compounds **28** wherein n is 0. First, Esters **31**, wherein R⁸ is as defined above, are synthesized by oxidation of mono-protected diols **X** in the presence of R⁸OH (see generally, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1196). An exemplary procedure for such an oxidation is described in Stevens *et al.*, 1982, *Tetrahedron Lett.* 23:4647 (HOCl); Sundararaman *et al.*, 1978, *Tetrahedron Lett.* 1627 (O₃/KOH); Wilson *et al.*, 1982, *J. Org. Chem.* 47:1360 (*t*-BuOOH/Et₃N); and Williams *et al.*, 1988, *Tetrahedron Lett.* 29:5087 (Br₂), the four of which citations are incorporated by reference herein. Compounds **31** are converted to compounds **28** wherein n is 0 by adapting the synthetic procedures depicted in Scheme 1.

Scheme 5: Synthesis of Compounds of Formula 18c, which correspond to compounds $W^{(1)(2)}-Z_m-OH$, Where $W^{(1)(2)}$ is $C(R^1)(R^2)-(CH_2)_cC(R^3)(R^4)-Y$

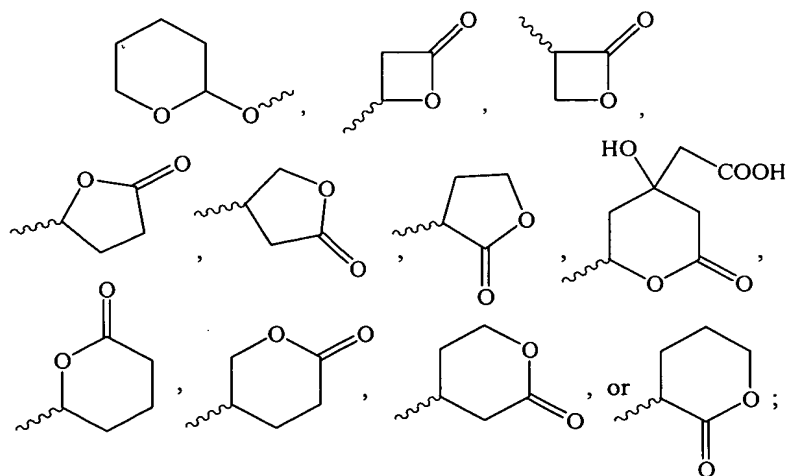


- Scheme 5 outlines methodology for the synthesis of protected alcohols **32** and alcohols **18c**, which correspond to $W^{(1)(2)}-Z_m-OPG$ and $W^{(1)(2)}-Z_m-OH$, respectively, wherein $W^{(1)(2)}$ is $C(R^1)(R^2)-(CH_2)_cC(R^3)(R^4)-Y$. The synthesis of starting materials **28**, **30** and **31** are depicted in Scheme 4 and the synthetic methods and procedures can be adapted from those described for Scheme 2.

Scheme 6: Synthesis of Compounds of Formula 18d, which correspond to compounds $W^{(1)(2)}-Z_m-OH$, Wherein $W^{(1)(2)}$ is $C(R^1)(R^2)(CH_2)_c-V$ where V is a Lactone Group

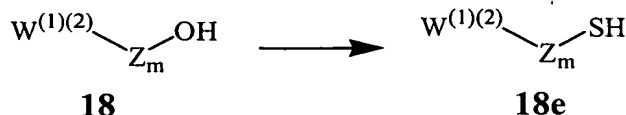


- Scheme 6 depicts the synthesis of protected lactone alcohols **34** and lactone alcohols **18d**. Compounds **34** and **18d** correspond to compounds of the formula, which correspond to compounds $W^{(1)(2)}-Z_m-OH$, Wherein $W^{(1)(2)}$ is $C(R^1)(R^2)(CH_2)_c-V$ and V is a Group selected from:



As shown in Scheme 6, protected lactone alcohols **34** and lactone alcohols **18d** can be synthesized from compounds of the formula **10**, **15**, or **16** by adaptation of the methods and procedures discussed above for Scheme 3.

Scheme 7: Conversion of Alcohols 18 to Thiols 18e

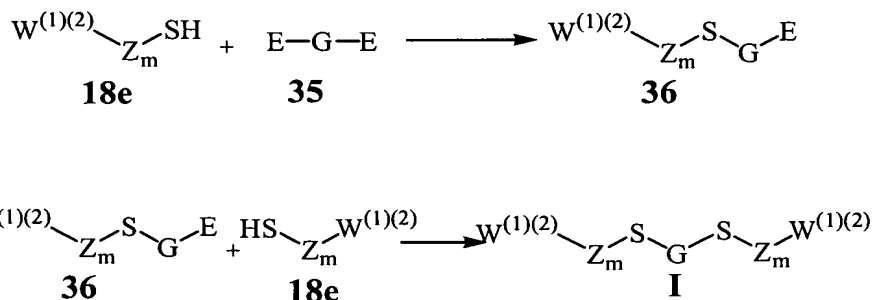


Scheme 7 depicts the synthesis of thiol **18e**. Thiol **18e** can be synthesized by a variety of methods. One method involves treatment of alcohols **18** with H₂S with a catalyst such as Al₂O₃; however, this method is limited to primary alcohols as described in Lucien *et al. Nouv. J. Chim.* **1979**, 3, 15, incorporated herein by reference. Another method involves treatment of alcohols **18** with Lawesson's reagent as described in Nishio, *J. Chem. Soc., Chem. Commun.* **1989**, 205, incorporated herein by reference. Still another method can be applied to primary, secondary, allylic, and benzylic alcohols using a fluoropyridinium salt and sodium N,N-dimethylthiocarbamate. See Hojo *et al. Chem. Lett.* **1977**, 133, 437. See also Alper, *J. Org. Chem.* **1988**, 53, 3306, incorporated herein by reference. A general method for converting vinyl and phenyl alcohols to thiols involves initially converting the alcohol to a leaving group (*e.g.*, a tosylate) then treating with a mercaptyl nucleophile (*e.g.*, sodium sulfhydryde, *i.e.*, NaSH). Protected alcohols **18** are further converted to the appropriate haloderivatives **18f**, as described in Larock, R. C., *Comprehensive Organic Transformations*, Wiley: New York 1999, p. 689-701. The haloderivatives are isolated or subsequently treated as a crude with sodium sulfhydryde equivalent (Wardell, P. *The Chemistry of the Thiol Group*, Patai, S., Ed.; Wiley: New York 1974, Pt. 1, p. 179-211), such as thiourea, 1,8-diazabicyclo[5.4.0]undec-7-ene (Ono, N., *et al. Synthesis* 1980, 952), tributylhexadecylphosphonium bromide (Landini, D. *Organic Syntheses Coll. Vol. 6*, Wiley: New York 1988, p. 833), or using the general procedures referenced in March, J. *Advanced Organic Chemistry: Reaction Mechanisms, and Structure*, Wiley: New York 1992, 4th ed., p. 406-407.

As outlined in Scheme 7, haloderivatives **18f** are also reacted with thiolate anions or sodium sulfide to produce compounds of type **II**. A typical procedure consists in the treatment of the halide with sodium sulfide in solvents such as water and alcohols, or mixtures of alcohol-water, at temperatures ranging between -20 °C to 100 °C, preferably refluxing ethanol-water, and reaction times from 1 hour to 48 hours (McAllen, D.T. *et. al.*,

J. Am. Chem. Soc. 1951, 101, 1805). The reaction are carried out using either halides or their Grignard reagents as described in the general procedures referenced in March, J/ *Advanced Organic Chemistry: Reaction Mechanisms, and Structure*, Wiley: New York 1992, 4th ed., p. 407-408, 613-614. Symmetrical sulfides **II** are also prepared by a thiosilane mediated synthesis starting from halides **18f** (Ando, W. *et al. Synth Commun.* 1982, 12, 627). In a typical procedure, dry sodium methoxide and hexamethyldisilathiane (Me₃Si)₂S in a soluble solvent, such as diethyl ether, diisopropyl ether, t-butyl-methyl ether, THF, toluene, or mixtures of solvents, preferably THF, are treated with halide **18f** in inert conditions at temperatures ranging from -20 °C to 50 °C and reaction times from 1 hour to 48 hours. The workup of the resulting reaction mixture is performed when the reaction is complete, which is determined by using the appropriate analytical method, such as thin-layer chromatography or HPLC. Thioderivatives **II** are isolated from the reaction mixture by methods well-known in the art, such as chromatography, distillation or recrystallization.

Scheme 8: Synthesis of Compounds of Formula I



Scheme 8 outlines the synthesis of compounds **I**. In the first step, compounds **36** are synthesized by reacting compounds **18e** (compounds **18 a,b,c**, and **d** are encompassed by **18e**) with compounds **35** under the conditions suitable for nucleophilic substitution. The conditions and methods discussed in Scheme 1 above for the synthesis of mono-protected diols **10** from alcohols **9** can be adapted for the synthesis of compounds **36**. Compounds **35**, wherein E is a suitable leaving group as defined above, preferably chloride or bromide, are readily obtained commercially (*e.g.*, Aldrich Chemical Co. Milwaukee WI) or by well known synthetic methods. Compounds **I** are obtained by reacting compounds **36** with compounds **18e** under the conditions suitable for nucleophilic substitution. In a preferred procedure, first, a base is added to a stirred organic solution comprising thiols **18e**, maintained at a constant temperature within the range of about 0°C to about 80°C, preferably at about room temperature. Preferably, the base is added at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial

reaction-mixture temperature. The base can be added as an organic solution or in undiluted form. Preferably, the base has a pK_a of about 10 or greater. Suitable bases include, but are not limited to, hydroxides, such as sodium hydroxide, potassium hydroxide, sodium carbonate, calcium hydroxide, magnesium hydroxide, alkylmetal bases such as

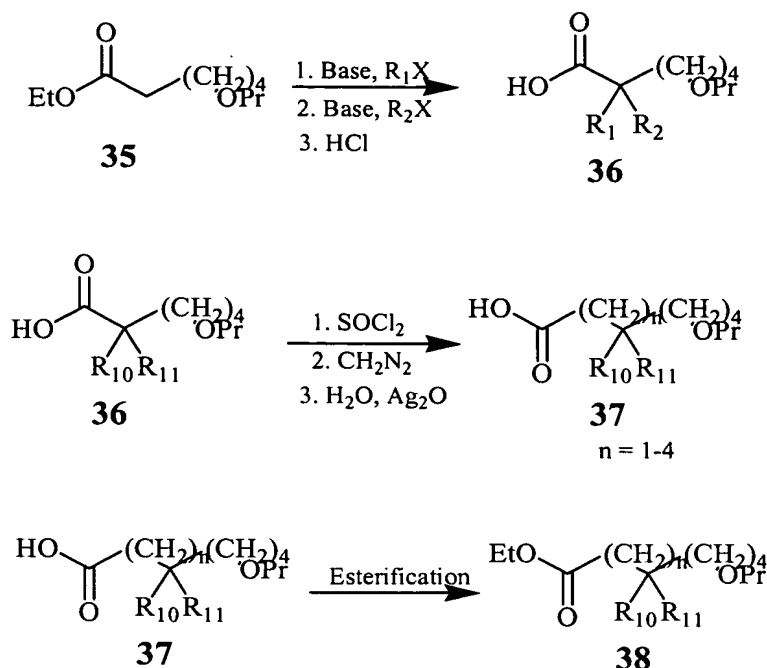
5 methyl lithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride.

10 The preferred base is sodium hydroxide. Suitable solvents include, but are not limited, to dimethyl sulfoxide, dichloromethane, ethers, and mixtures thereof, preferably tetrahydrofuran. After addition of the base, the reaction mixture is adjusted to within a temperature range of about 0°C to about room temperature and compounds **35** are added, preferably at a rate such that the reaction-mixture temperature remains within about one to

15 two degrees of the initial reaction-mixture temperature. Compounds **35** can be diluted in an organic solvent or added in undiluted form. The resulting reaction mixture is heated at a constant temperature within the range of about room temperature to about the solvent's boiling temperature until the reaction is substantially complete as determined by using an appropriate analytical method, preferably by thin-layer chromatography or gas

20 chromatography. Compound **36** can be isolated by workup and purification. Compound **36** thus obtained is treated in the same conditions with an equivalent of compound **18e**, and the product **I** is separated from the reaction mixture by the usual separation methods, such as recrystallization, distillation, or chromatography.

Scheme 9: Synthesis of Compounds II



Scheme 9 illustrates the alpha disubstitution of an ester containing a terminal protected hydroxyl moiety. Compounds that contain strong electron withdrawing groups are easily converted to the corresponding enolates. These enolate ions can readily attack an electrophile resulting in alpha substitution. *See Some Modern Methods of Organic Synthesis*, 3rd Ed.; Cambridge University Press: Cambridge, 1986, pp. 1-26, incorporated herein by reference. The reaction is successful for primary and secondary alkyl, allylic, and benzylic groups. The use of polar aprotic solvents, *e.g.*, dimethylformamide or dimethylsulfoxide, is preferred. Phase transfer catalysts can also be used. *See Tundo et al. J. Chem. Soc., Perkin Trans. 1*, **1987**, 2159, which is incorporated herein by reference.

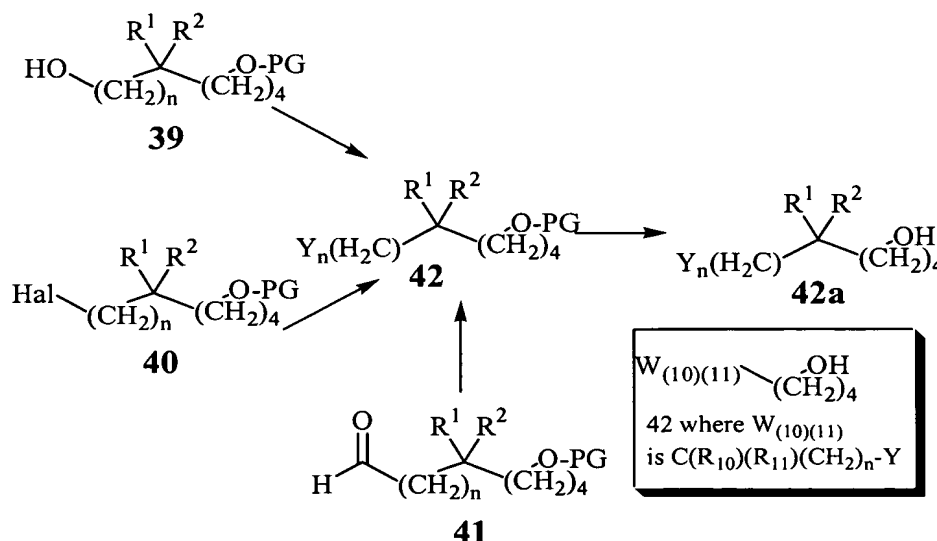
Esters used as starting materials for enolate alkylations are prepared by methods well-known in the field and recently reviewed by J. Muelzer in *Comprehensive Organic Functional Group Transformations*, A. R. Katritzky, O. Meth-Cohn and C. W. Rees, Eds., Pergamon: Oxford 1995, p. 122-160. Particularly, esters with R¹R² as a cyclopropyl group are prepared by methods summarized by T. Saegusa et al., *Synthesis* 1975, 291. Esters with R¹R² as a cyclopentyl group are prepared by reductive cyclization of diiodopropanes or other 1,3-diiodides with acrylic esters (T. Saegusa et al. *J. Org. Chem.* **1974**, 39, 3273). Cyclohexyl esters are conveniently prepared via Dieckman condensation, which is particularly suitable for annulation even in sophisticated substitutions (J. Bosch et al., *J. Org. Chem.* **1981**, 46, 1538, A. G. Pearson, *J. Chem. Soc., Perkins Trans 1* **1979**, 1979). Diels-Alder additions are preferred for cyclohexenoates, also for cyclohexanoates with a

particular stereoselectivity. When R^1 =Aryl, alkylation with R^2 is facilitated (E.M. Kaiser *et al.* in *Organic Syntheses Coll. Vol. 5*, Wiley: New York 1973, p. 559). Non-symmetrical diaklysubstituted esters are prepared by esterification of the corresponding acids, available from halides R^1R^2CHX , via Grignard reactions (H. Gilman *et al.* in *Organic Syntheses Coll. Vol. 1*, Wiley: New York 1932, p. 361).

The homologation of carboxylic acids is feasible by methods well-known in the art and summarized by the sequences: $COOH \rightarrow CH_2OH \rightarrow CH_2Hal \rightarrow CH_2CN \rightarrow CH_2COOH$ or $COOH \rightarrow CH_2OH \rightarrow CH_2Hal \rightarrow CH_2MgHal \rightarrow CH_2COOH$. The transformation of an acid to the corresponding alcohol is performed using the general procedures referenced in Larock, R. C., *Comprehensive Organic Transformations*, Wiley: New York 1999, p. 1114-1123. For halogenation of alcohols, see *ibid.* 689-697. The conversion of halides to carboxylic acids are described in Vogel, A. I. *Textbook of Practical Organic Chemistry*, Longman Scientific & Technical – Wiley: New York, 19889, p. 664-691.

The conversion to a carboxylic acid with an additional carbon is achieved by treating an acyl halide with diazomethane to generate an intermediate diazo ketone, which in the presence of water and silver oxide rearranges through a ketene intermediate to a carboxylic acid with an additional carbon atom **37**. If the reaction is done in an alcohol instead of water an ester is recovered. See Meier *et al.* *Angew. Chem. Int. Ed. Eng.* 1975, 14, 32-43, which is incorporated herein by reference. Alternatively, the carboxylic acid can be esterified by known techniques. The reaction can be repeated to generate methylene groups adjacent to the carboxylic acid.

Scheme 10: Synthesis of Compounds of Formula 42a which correspond to Compounds $W_{(10)(11)}-(CH_2)_4-OH$, wherein $W_{(10)(11)}$ is $C(R_{10})(R_{11})(CH_2)_nY$

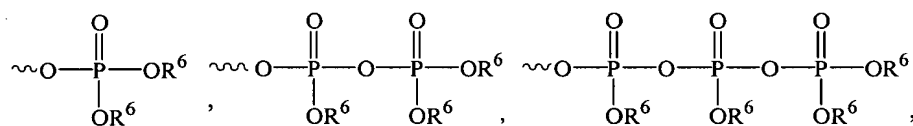


Scheme 10 outlines methodology for the synthesis of protected alcohols **42a** wherein Y, R¹, R², Z, and m are defined as above. Protected alcohols **42a** correspond to compounds of the formula W⁽¹⁾⁽²⁾-Zm-OPG, wherein W⁽¹⁾⁽²⁾ is C(R¹)(R²)-Y.

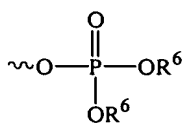
Protected alcohols **42**, wherein Y comprises a -C(O)OH group, can be synthesized
5 by oxidizing mono-protected diols **39** with an agent suitable for oxidizing a primary alcohol to a carboxylic acid (for a discussion see M. Hudlicky, *Oxidations in Organic Chemistry*, ACS Monograph 186, 1990, pp. 127-130, incorporated by reference herein). Suitable oxidizing agents include, but are not limited to, pyridinium dichromate (Corey *et al.*, 1979, *Tetrahedron Lett.* 399); manganese dioxide (Ahrens *et al.*, 1967, *J. Heterocycl. Chem.* 4:625); sodium permanganate monohydrate (Menger *et al.*, 1981, *Tetrahedron Lett.* 22:1655); and potassium permanganate (Sam *et al.*, 1972, *J. Am. Chem. Soc.* 94:4024), all of which citations are incorporated by reference herein. The preferred oxidizing reagent is pyridinium dichromate. In an alternative synthetic procedure, protected alcohols **42**, wherein Y comprises a -C(O)OH group, can be synthesized by treatment of protected halo-
10 alcohols **40**, wherein X is iodo, with CO or CO₂, as described in Bailey *et al.*, 1990, *J. Org. Chem.* 55:5404 and Yanagisawa *et al.*, 1994, *J. Am. Chem. Soc.* 116:6130, the two of which citations are incorporated by reference herein. Protected alcohols **42**, wherein Y comprises -C(O)OR⁵, wherein R⁵ is as defined above, can be synthesized by oxidation of mono-protected diols **39** in the presence of R⁵OH (see generally, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1196). An exemplary
20 procedure for such an oxidation is described in Stevens *et al.*, 1982, *Tetrahedron Lett.* 23:4647 (HOCl); Sundararaman *et al.*, 1978, *Tetrahedron Lett.* 1627 (O₃/KOH); Wilson *et al.*, 1982, *J. Org. Chem.* 47:1360 (*t*-BuOOH/Et₃N); and Williams *et al.*, 1988, *Tetrahedron Lett.* 29:5087 (Br₂), the four of which citations are incorporated by reference herein. Preferably, protected alcohols **42**, wherein Y comprises a -C(O)OR⁵ group are synthesized
25 from the corresponding carboxylic acid (*i.e.*, **42**, wherein Y comprises -C(O)OH) by esterification with R⁵OH (*e.g.*, see March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 393-394, incorporated by reference herein). In another alternative synthesis, protected alcohols **42**, wherein Y comprises -C(O)OR⁵, can
30 be prepared from protected halo-alcohols **40** by carbonylation with transition metal complexes (*see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 484-486; Urata *et al.*, 1991, *Tetrahedron Lett.* 32:36, 4733); and Ogata *et al.*, 1969, *J. Org. Chem.* 3985, the three of which citations are incorporated by reference herein).

Protected alcohols **42**, wherein Y comprises $-\text{OC}(\text{O})\text{R}^5$, wherein R^5 is as defined above, can be prepared by acylation of mono-protected diols **39** with a carboxylate equivalent such as an acyl halide (*i.e.*, $\text{R}^5\text{C}(\text{O})-\text{Hal}$, wherein Hal is iodo, bromo, or chloro, *see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392 and *Org. Synth. Coll. Vol. III*, Wiley, NY, pp. 142, 144, 167, and 187 (1955)) or an anhydride (*i.e.*, $\text{R}^5\text{C}(\text{O})-\text{O}-(\text{O})\text{CR}^5$, *see e.g.*, March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 392-393 and *Org. Synth. Coll. Vol. III*, Wiley, NY, pp. 11, 127, 141, 169, 237, 281, 428, 432, 690, and 833 (1955), all of which citations are incorporated herein by reference). Preferably, the reaction is conducted by adding a base to a solution comprising mono-protected diols **39**, a carboxylate equivalent, and an organic solvent, which solution is preferably maintained at a constant temperature within the range of 0°C to about room temperature. Solvents suitable for reacting mono-protected diols **39** with a carboxylate equivalent include, but are not limited to, dichloromethane, toluene, and ether, preferably dichloromethane. Suitable bases include, but are not limited to, hydroxide sources, such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate; or an amine such as triethylamine, pyridine, or dimethylaminopyridine. The progress of the reaction can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols **42**, wherein Y comprises one of the following phosphate ester groups

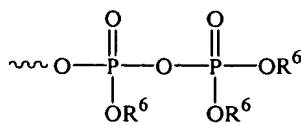


wherein R^6 is defined as above, can be prepared by phosphorylation of mono-protected diols **10** according to well-known methods (for a general reviews, *see Corbridge Phosphorus: An Outline of its Chemistry, Biochemistry, and Uses*, Studies in Inorganic Chemistry, 3rd ed., pp. 357-395 (1985); Ramirez *et al.*, 1978, *Acc. Chem. Res.* **11**:239; and Kalckare *Biological Phosphorylations*, Prentice-Hall, New York (1969); J. B. Sweeny in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 2, pp. 104-109, the four of which are incorporated herein by reference). Protected alcohols **42** wherein Y comprises a monophosphate group of the formula:

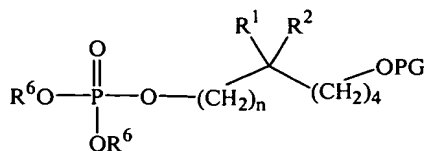


wherein R⁶ is defined as above, can be prepared by treatment of mono-protected diol **39** with phosphorous oxychloride in a suitable solvent, such as xylene or toluene, at a constant temperature within the range of about 100°C to about 150°C for about 2 hours to about 24 hours. After the reaction is deemed substantially complete, by using an appropriate analytical method, the reaction mixture is hydrolyzed with R⁶-OH. Suitable procedures are referenced in Houben-Weyl, Methoden der Organische Chemie, Georg Thieme Verlag Stuttgart 1964, vol. 12/2, pp. 143-210 and 872-879, incorporated by reference herein. Alternatively, when both R⁶ are hydrogen, can be synthesized by reacting mono-protected diols **10** with silyl polyphosphate (Okamoto *et al.*, 1985, *Bull Chem. Soc. Jpn.* 58:3393, incorporated herein by reference) or by hydrogenolysis of their benzyl or phenyl esters (Chen *et al.*, 1998, *J. Org. Chem.* 63:6511, incorporated herein by reference). In another alternative procedure, when R⁶ is (C₁-C₆)alkyl, (C₂-C₆)alkenyl, or (C₂-C₆)alkynyl, the monophosphate esters can be prepared by reacting mono-protected diols **39** with appropriately substituted phosphoramidites followed by oxidation of the intermediate with *m*-chloroperbenzoic acid (Yu *et al.*, 1988, *Tetrahedron Lett.* 29:979, incorporated herein by reference) or by reacting mono-protected diols **39** with dialkyl or diaryl substituted phosphorochloridates (Pop, *et al.*, 1997, *Org. Prep. and Proc. Int.* 29:341, incorporated herein by reference). The phosphoramidites are commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or readily prepared according to literature procedures (*see e.g.*, Uhlmann *et al.* 1986, *Tetrahedron Lett.* 27:1023 and Tanaka *et al.*, 1988, *Tetrahedron Lett.* 29:199, both of which are incorporated herein by reference). The phosphorochloridates are also commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared according to literature methods (*e.g.*, Gajda *et al.*, 1995, *Synthesis* 25:4099. In still another alternative synthesis, protected alcohols **42**, wherein Y comprises a monophosphate group and R⁶ is alkyl or aryl, can be prepared by reacting IP⁺(OR⁶)₃ with mono-protected diols **39** according to the procedure described in Stowell *et al.*, 1995, *Tetrahedron Lett.* 36:11, 1825 or by alkylation of protected halo alcohols **40** with the appropriate dialkyl or diaryl phosphates (*see e.g.*, Okamoto, 1985, *Bull Chem. Soc. Jpn.* 58:3393, incorporated herein by reference).

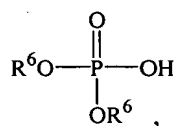
Protected alcohols **42** wherein Y comprises a diphosphate group of the formula



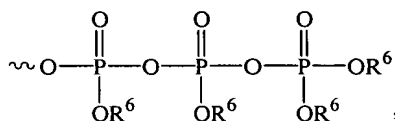
wherein R^6 is defined as above, can be synthesized by reacting the above-discussed monophosphates of the formula:



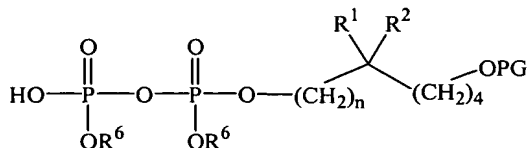
5 with a phosphate of the formula



(commercially available, e.g., Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of carbodiimide such as dicyclohexylcarbodiimide, as described in Houben-Weyl, *Methoden der Organische Chemie*, Georg Thieme Verlag Stuttgart 1964, vol. 12/2, pp. 881-10 885. In the same fashion, protected alcohols **42**, wherein Y comprises a triphosphate group of the formula:

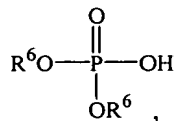


can be synthesized by reacting the above-discussed diphosphate protected alcohols, of the formula:



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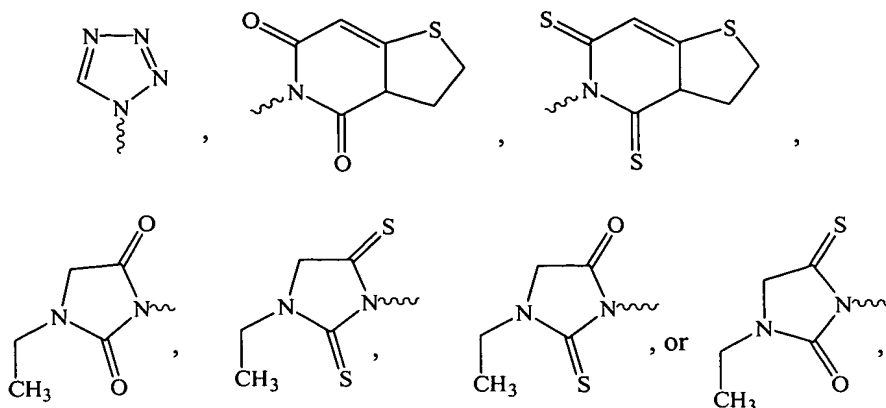
with a phosphate of the formula:



as described above. Alternatively, when R^6 is H, protected alcohols **42** wherein Y comprises the triphosphate group, can be prepared by reacting mono-protected diols **39** with

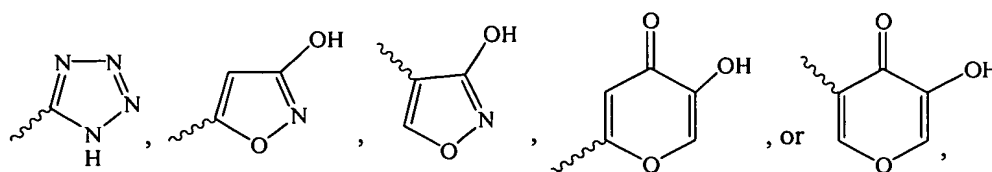
salicyl phosphorochloridite and then pyrophosphate and subsequent cleavage of the adduct thus obtained with iodine in pyridine as described in Ludwig *et al.*, 1989, *J. Org. Chem.* 54:631, incorporated herein by reference.

5 Protected alcohols **42**, wherein Y is $-\text{SO}_3\text{H}$ or a heterocyclic group selected from the group consisting of:



can be prepared by halide displacement from protected halo-alcohols **40**. Thus, when Y is $-\text{SO}_3\text{H}$, protected alcohols **42** can be synthesized by reacting protected halo-alcohols **40** with sodium sulfite as described in Gilbert *Sulfonation and Related Reactions*; Wiley: New York, 10 1965, pp. 136-148 and pp. 161-163; *Org. Synth. Coll.* Vol. II, Wiley, NY, 558, 564 (1943); and *Org. Synth. Coll.* Vol. IV, Wiley, NY, 529 (1963), all three of which are incorporated herein by reference. When Y is one of the above-mentioned heterocycles, protected alcohols **42** can be prepared by reacting protected halo-alcohols **40** with the corresponding heterocycle in the presence of a base. The heterocycles are available commercially (*e.g.*, 15 Aldrich Chemical Co., Milwaukee, Wisconsin) or prepared by well-known synthetic methods (see the procedures described in Ware, 1950, *Chem. Rev.* 46:403-470, incorporated herein by reference). Preferably, the reaction is conducted by stirring a mixture comprising **40**, the heterocycle, and a solvent at a constant temperature within the range of about room temperature to about 100°C , preferably within the range of about 50°C to about 70°C for 20 about 10 to about 48 hours. Suitable bases include hydroxide bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, or potassium carbonate. Preferably, the solvent used in forming protected alcohols **42** is selected from dimethylformamide; formamide; dimethyl sulfoxide; alcohols, such as methanol or ethanol; and mixtures thereof. The progress of the reaction can be followed by using an appropriate analytical technique, 25 such as thin layer chromatography or high performance liquid chromatography and when substantially complete, the product can be isolated by workup and purified if desired.

Protected alcohols **42**, wherein Y is a heteroaryl ring selected from

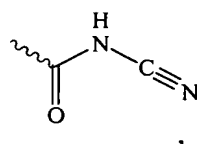


can be prepared by metallating the suitable heteroaryl ring then reacting the resulting metallated heteroaryl ring with protected halo-alcohols **40** (for a review, see Katritzky
5 *Handbook of Heterocyclic Chemistry*, Pergamon Press: Oxford 1985). The heteroaryl rings are available commercially or prepared by well-known synthetic methods (*see e.g.*, Joule *et al.*, *Heterocyclic Chemistry*, 3rd ed., 1995; De Sarlo *et al.*, 1971, *J. Chem. Soc. (C)* **86**; Oster *et al.*, 1983, *J. Org. Chem.* **48**:4307; Iwai *et al.*, 1966, *Chem. Pharm. Bull.* **14**:1277; and United States Patent No. 3,152,148, all of which citations are incorporated herein by
10 reference). As used herein, the term “metallating” means the forming of a carbon-metal bond, which bond may be substantially ionic in character. Metallation can be accomplished by adding about 2 equivalents of strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the heterocycle. Two equivalents of base are required: one
15 equivalent of the base deprotonates the –OH group or the –NH group, and the second equivalent metallates the heteroaryl ring. Alternatively, the hydroxy group of the heteroaryl ring can be protected with a base-stable, acid-labile protecting group as described in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), incorporated herein by reference. Where the hydroxy group is protected, only one equivalent of base is
20 required. Examples of suitable base-stable, acid-labile hydroxyl-protecting groups, include but are not limited to, ethers, such as methyl, methoxy methyl, methylthiomethyl, methoxyethoxymethyl, *bis*(2-chloroethoxy)methyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, tetrahydrothiofuranyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, *t*-butyl, allyl, benzyl, *o*-nitrobenzyl, triphenylmethyl, α -
25 naphthyl diphenylmethyl, *p*-methoxyphenyl diphenylmethyl, 9-(9-phenyl-10-oxo)anthranyl, trimethylsilyl, isopropyl dimethylsilyl, *t*-butyl dimethylsilyl, *t*-butyl diphenylsilyl, tribenzylsilyl, triisopropylsilyl; and esters, such as pivaloate, adamantate, and 2,4,6-trimethylbenzoate. Ethers are preferred, particularly straight chain ethers, such as methyl ether, methoxymethyl ether, methylthiomethyl ether, methoxyethoxymethyl ether, *bis*(2-chloroethoxy)methyl ether. Preferably, the pK_a of the base is higher than the pK_a of the
30 proton of the heterocycle to be deprotonated. For a listing of pK_a s for various heteroaryl

rings, see Fraser *et al.*, 1985, *Can. J. Chem.* 63:3505, incorporated herein by reference. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride. If desired, the organometallic base can be activated with a complexing agent, such as *N,N,N',N'*-tetramethylethylenediamine or hexamethylphosphoramide (1970, *J. Am. Chem. Soc.* 92:4664, incorporated by reference herein). Solvents suitable for synthesizing protected alcohols **42**, wherein Y is a heteroaryl ring include, but are not limited to, diethyl ether; tetrahydrofuran; and hydrocarbons, such as pentane. Generally, metallation occurs alpha to the heteroatom due to the inductive effect of the heteroatom, however, modification of conditions, such as the identity of the base and solvents, order of reagent addition, reagent addition times, and reaction and addition temperatures can be modified by one of skill in the art to achieve the desired metallation position (*see e.g.*, Joule *et al.*, *Heterocyclic Chemistry*, 3rd ed., 1995, pp. 30-42, incorporated by reference herein) Alternatively, the position of metallation can be controlled by use of a halogenated heteroaryl group, wherein the halogen is located on the position of the heteroaryl ring where metallation is desired (*see e.g.*, Joule *et al.*, *Heterocyclic Chemistry*, 3rd ed., 1995, p. 33 and Saulnier *et al.*, 1982, *J. Org. Chem.* 47:757, the two of which citations are incorporated by reference herein). Halogenated heteroaryl groups are available commercially (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin) or can be prepared by well-known synthetic methods (*see e.g.*, Joule *et al.*, *Heterocyclic Chemistry*, 3rd ed., 1995, pp. 78, 85, 122, 193, 234, 261, 280, 308, incorporated by reference herein). After metallation, the reaction mixture comprising the metallated heteroaryl ring is adjusted to within a temperature range of about 0°C to about room temperature and protected halo-alcohols **40** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. After addition of protected halo-alcohols **40**, the reaction mixture is stirred at a constant temperature within the range of about room temperature and about the solvent's boiling temperature and the reaction's progress can be monitored by the appropriate analytical technique, preferably thin-layer chromatography or high-performance liquid chromatography. After the reaction is substantially complete, protected alcohols **42** can be isolated by workup and purification.

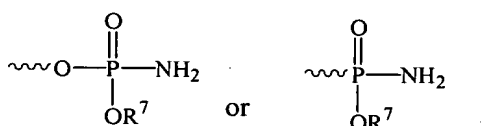
It is to be understood that conditions, such as the identity of protected halo-alcohol **40**, the base, solvents, orders of reagent addition, times, and temperatures, can be modified by one of skill in the art to optimize the yield and selectivity. Exemplary procedures that can be used in such a transformation are described in Shirley *et al.*, 1995, *J. Org. Chem.* 20:225; Chadwick *et al.*, 1979, *J. Chem. Soc., Perkin Trans. 1* 2845; Rewcastle, 1993, *Adv. Het. Chem.* 56:208; Katritzky *et al.*, 1993, *Adv. Het. Chem.* 56:155; and Kessar *et al.*, 1997, *Chem. Rev.* 97:721.

When Y is

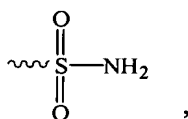


protected alcohols **42** can be prepared from their corresponding carboxylic acid derivatives (**42**, wherein Y is $\text{---CO}_2\text{H}$) as described in Belletire *et al.*, 1988, *Synthetic Commun.* 18:2063 or from the corresponding acylchlorides (**42**, wherein Y is ---CO---halo) as described in Skinner *et al.*, 1995, *J. Am. Chem. Soc.* 77:5440, both citations are incorporated herein by reference. The acylhalides can be prepared from the carboxylic acids by well known procedures such as those described in March, J., *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 437-438, incorporated by reference herein.

When Y is



wherein R^7 is as defined above, protected alcohols **42** can be prepared by first reacting protected halo-alcohols **40** with a trialkyl phosphite according to the procedure described in Kosolapoff, 1951, *Org. React.* 6:273 followed by reacting the derived phosphonic diester with ammonia according to the procedure described in Smith *et al.*, 1957, *J. Org. Chem.* 22:265, incorporated herein by reference. When Y is



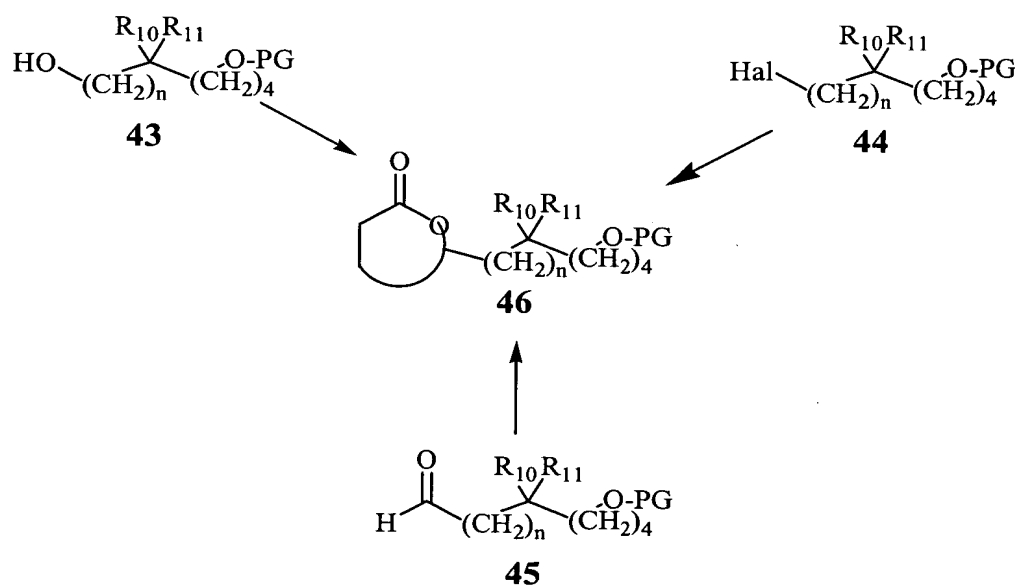
protected alcohols **42** can be prepared by reacting their sulphonic acid derivatives (*i.e.*, **42**, wherein Y is $\text{---SO}_3\text{H}$) with ammonia as described in Sianesi *et al.*, 1971, *Chem. Ber.*

104:1880 and Campagna *et al.*, 1994, *Farmaco, Ed. Sci.* 49:653, both of which citations are incorporated herein by reference).

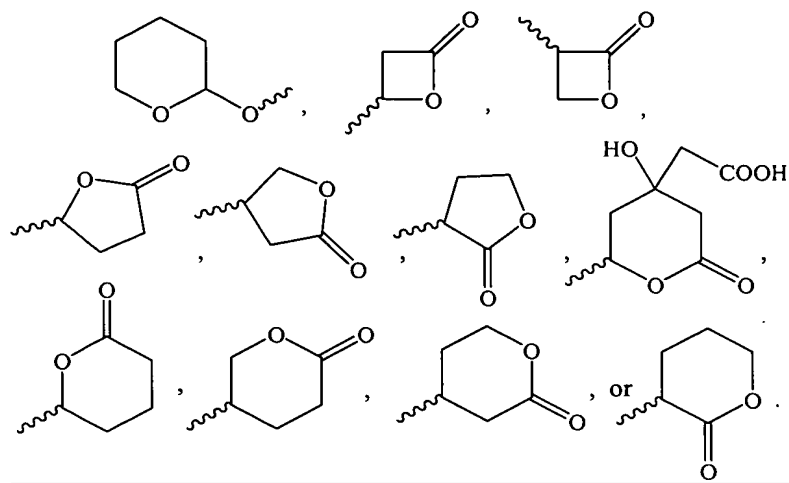
As further illustrated in Scheme 2, protected alcohols **42** can be deprotected providing alcohols **42a**. The deprotection method depends on the identity of the alcohol-protecting group, *see e.g.*, the procedures listed in Greene, T.W., *Protective Groups in Organic Synthesis*, 3rd edition 17-237 (1999), particularly see pages 48-49, incorporated herein by reference. One of skill in the art will readily be able to choose the appropriate deprotection procedure. When the alcohol is protected as an ether function (*e.g.*, methoxymethyl ether), the alcohol is preferably deprotected with aqueous or alcoholic acid.

Suitable deprotection reagents include, but are not limited to, aqueous hydrochloric acid, *p*-toluenesulfonic acid in methanol, pyridinium-*p*-toluenesulfonate in ethanol, Amberlyst H-15 in methanol, boric acid in ethylene-glycol-monoethylether, acetic acid in a water-tetrahydrofuran mixture, aqueous hydrochloric acid is preferred. Examples of such procedures are described, respectively, in Bernady *et al.*, 1979, *J. Org. Chem.* 44:1438; Miyashita *et al.*, 1977, *J. Org. Chem.* 42:3772; Johnston *et al.*, 1988, *Synthesis* 393; Bongini *et al.*, 1979, *Synthesis* 618; and Hoyer *et al.*, 1986, *Synthesis* 655; Gigg *et al.*, 1967, *J. Chem. Soc. C*, 431; and Corey *et al.*, 1978, *J. Am. Chem. Soc.* 100:1942, all of which are incorporated herein by reference.

Scheme 11: Synthesis of Compounds of Formula 46 which correspond to Compounds $W_{(10)(11)}-(CH_2)_4-OH$, wherein $W_{(10)(11)}$ is $C(R_{10})(R_{11})(CH_2)_4$ -Lactone

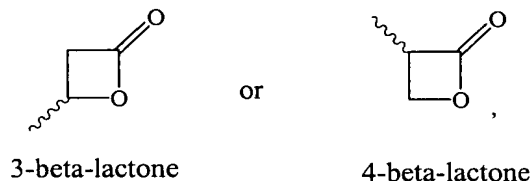


Scheme 11 depicts the synthesis of protected lactone alcohols **46** and lactone. Compound **46** corresponds to compounds of the formula $W^{(1)(2)}\text{-Zm-OPG}$ and , wherein $W^{(1)(2)}$ is a lactone group selected from:

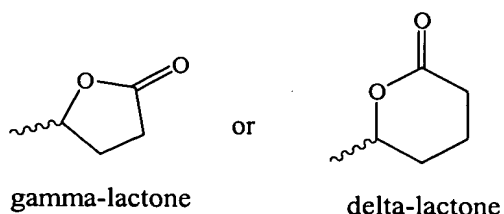


- 5 Protected lactone alcohols **46** can be prepared from compounds of the formula **43**, **45**, or **44** by using well-known condensation reactions and variations of the Michael reaction. Methods for the synthesis of lactones are disclosed in Multzer in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 5, pp. 161-173, incorporated herein by reference. Mono-
10 protected diols **43**, electrophilic protected alcohols **44**, and aldehydes **45** are readily available ether commercially (e.g., Aldrich Chemical Co., Milwaukee, WI) or by well known synthetic procedures.

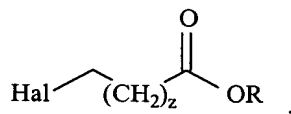
When $W^{(1)(2)}$ is a beta-lactone group of the formula:



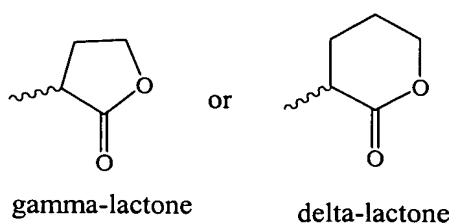
- 15 protected lactone alcohols **46** can be prepared from aldehydes **45** and electrophilic protected alcohols **44**, respectively, by a one-pot-addition-lactonization according to the procedure of Masamune *et al.*, 1976, *J. Am. Chem. Soc.* **98**:7874 and Danheiser *et al.*, 1991, *J. Org. Chem.* **56**:1176, both of which are incorporated herein by reference. This one-pot-addition-lactonization methodology has been reviewed by Multzer in *Comprehensive Organic Functional Group Transformations*, A.R. Katritzky, O. Meth-Cohn and C.W. Rees, Eds. Pergamon: Oxford, 1995, vol 5, pp. 161, incorporated herein by reference When $W^{(1)(2)}$ is a
20 gamma- or delta-lactone group of the formula:



protected lactone alcohols **46** can be prepared from aldehydes **45** according to well known synthetic methodology. For example, the methodology described in Masuyama *et al.*, 2000, *J. Org. Chem.* 65:494; Eisch *et al.*, 1978, *J. Organo. Met. Chem. C8* 160; Eaton *et al.*, 1947, *J. Org. Chem.* 37:1947; Yunker *et al.*, 1978, *Tetrahedron Lett.* 4651; Bhanot *et al.*, 1977, *J. Org. Chem.* 42:1623; Ehlinger *et al.*, 1980, *J. Am. Chem. Soc.* 102:5004; and Raunio *et al.*, 1957, *J. Org. Chem.* 22:570, all of which citations are incorporated herein by reference. For instance, as described in Masuyama *et al.*, 2000, *J. Org. Chem.* 65:494, aldehydes **45** can be treated with about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, in a suitable organic solvent to give a reaction mixture. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. The reaction-mixture temperature is adjusted to within the range of about 0°C to about 100°C, preferably about room temperature to about 50°C, and a halide of the formula:



wherein z is 1 or 2 (diluted with a solvent or in undiluted form) is added. The reaction mixture is stirred for a period of about 2 hours to about 48 hours, preferably about 5 to about 10 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **46** can be isolated by workup and purified if desired. When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:



protected lactone alcohols **46** can be synthesized by deprotonating the corresponding lactone with a strong base providing the lactone enolate and reacting the enolate with electrophilic protected alcohols **44** (for a detailed discussion of enolate formation of active

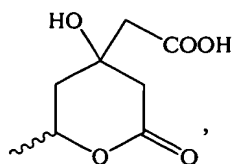
5 methylene compounds such as lactones, see House *Modern Synthetic Reactions*; W. A. Benjamin, Inc. Philippines 1972 pp. 492-570, and for a discussion of reaction of lactone enolates with electrophiles such as carbonyl compounds, see March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 944-945, both of which are incorporated herein by reference). Lactone-enolate formation can be accomplished by

10 adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the lactone. Suitable bases include, but are not limited to, alkylmetal bases such as methyl lithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium

15 amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyldisilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Solvents suitable for lactone-enolate formation include, but are not limited to, diethyl ether and

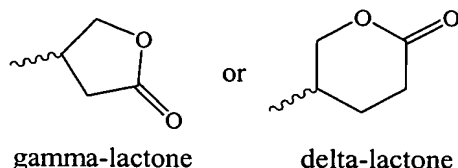
20 tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about -78°C to about room temperature, preferably about -50°C to about 0°C , and electrophilic protected alcohols **44** (diluted with a solvent or in undiluted form) are added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The reaction mixture is

25 stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, protected lactone alcohols **46** can be isolated by workup and purified if desired. When $W^{(1)(2)}$ is a lactone group of the formula:

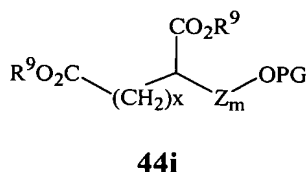


protected lactone alcohols **46** can be prepared from aldehydes **45** according to the procedure described in United States Patent No. 4,622,338, incorporated by reference herein.

When $W^{(1)(2)}$ is a gamma- or delta-lactone group of the formula:

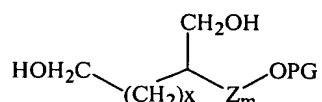


protected lactone alcohols **46** can be prepared according to a three step sequence. The first step comprises base-mediated reaction of electrophilic protected alcohols **44** with succinic acid esters (*i.e.*, $R^9O_2CCH_2CH_2CO_2R^9$, wherein R^9 is alkyl) or glutaric acid esters (*i.e.*, $R^9O_2CCH_2CH_2CH_2CO_2R^9$, wherein R^9 is alkyl) providing a diester intermediate of the formula **44i**:

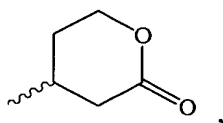


wherein x is 1 or 2 depending on whether the gamma or delta lactone group is desired. The reaction can be performed by adding about 1 equivalent of a strong organometallic base, preferably with a pK_a of about 25 or more, more preferably with a pK_a of greater than about 35, to a mixture comprising a suitable organic solvent and the succinic or glutaric acid ester. Suitable bases include, but are not limited to, alkylmetal bases such as methyllithium, *n*-butyllithium, *tert*-butyllithium, *sec*-butyllithium, phenyllithium, phenyl sodium, and phenyl potassium; metal amide bases such as lithium amide, sodium amide, potassium amide, lithium tetramethylpiperidide, lithium diisopropylamide, lithium diethylamide, lithium dicyclohexylamide, sodium hexamethyldisilazide, and lithium hexamethyl-disilazide; and hydride bases such as sodium hydride and potassium hydride, preferably lithium tetramethylpiperidide. Suitable solvents include, but are not limited to, diethyl ether and tetrahydrofuran. After enolate formation, the reaction-mixture temperature is adjusted to within the range of about -78°C to about room temperature, preferably about -50°C to about 0°C , and electrophilic protected alcohols **44** (diluted with a solvent or in undiluted form) are

added, preferably at a rate such that the reaction-mixture temperature remains within about one to two degrees of the initial reaction-mixture temperature. The reaction mixture is stirred for a period of about 15 minutes to about 5 hours, during which time the reaction's progress can be followed by using an appropriate analytical technique, such as thin layer chromatography or high performance liquid chromatography. When the reaction is deemed substantially complete, the diester intermediate can be isolated by workup and purified if desired. In the second step, the intermediate diester can be reduced, with a hydride reducing agent, to yield a diol:

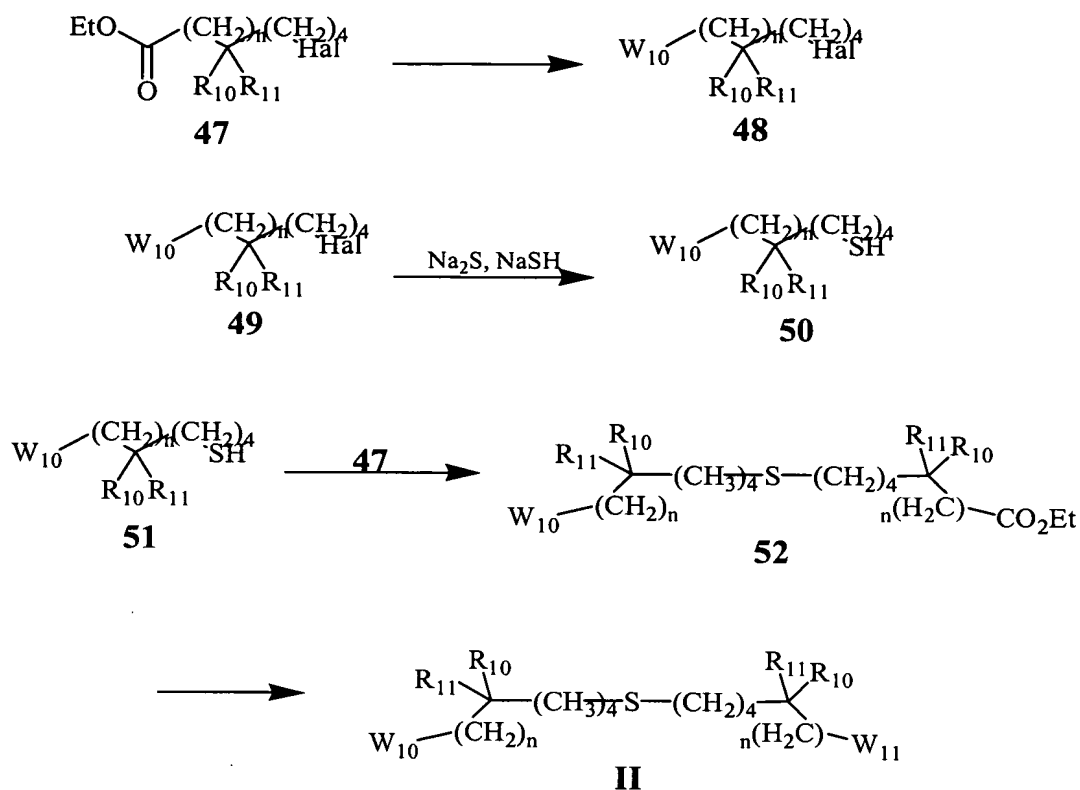


The reduction can be performed according to the procedures referenced in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, p. 1214, incorporated herein by reference). Suitable reducing agents include, but are not limited to, lithium aluminum hydride, diisobutylaluminum hydride, sodium borohydride, and lithium borohydride. In the third step, the diol can be oxidatively cyclized with $\text{RuH}_2(\text{PPh}_3)_4$ to the product protected lactone alcohols **46** according to the procedure of Yoshikawa *et al.*, 1986, *J. Org. Chem.* **51**:2034 and Yoshikawa *et al.*, 1983, *Tetrahedron Lett.* **26**:2677, both of which citations are incorporated herein by reference. When $\text{W}^{(1)(2)}$ is a lactone group of the formula:



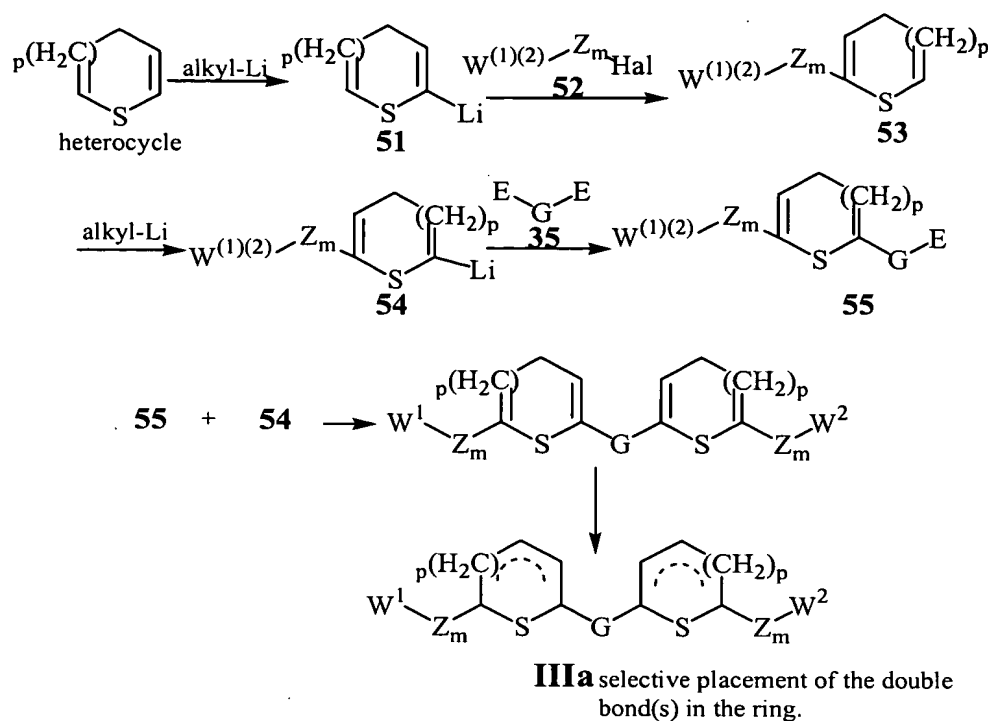
protected lactone alcohols **46** can be synthesized by reacting the Grignard salts of electrophilic protected alcohols **44**, where E is a halide, with 5,6-dihydro-2H-pyran-2-one, commercially available (*e.g.*, Aldrich Chemical Co., Milwaukee, Wisconsin), in the presence of catalytic amounts of a 1-dimethylaminoacetylpyrrolidine-2-yl)methyl-diarylphosphine-copper (I) iodide complex as described in Tomioka *et al.*, 1995, *Tetrahedron Lett.* **36**:4275, incorporated herein by reference.

Scheme 12: Synthesis of Compounds of Formula II



Scheme 12 illustrates the synthesis of sulfide **II**. The ester **47** is initially converted to the desired group W_{10} , which is defined above. Compound **48** is then treated with sodium sulfhydryde to form a thiol from the alkyl halide. See Wardell, in Patai *The Chemistry of the Thiol Group*, pt.1; Wiley: New York, 1974, pp. 179-211. The thiol is then condensed with halide **48** to form sulfide **52**. The ester in **52** is then converted to the desired group W_{11} , which is defined above, to afford **II**.

Scheme 13: Synthesis of Compounds III



Scheme 13 depicts the synthesis of compounds **III**, that is, compounds where a double bond is present in the ring. In the first step, the appropriate heterocycle is lithiated with an alkyl lithium base (alkyl-Li, e.g., butyl lithium) by well known synthetic methods (for a review, see Katritzky *Handbook of Heterocyclic Chemistry*, Pergamon Press: Oxford 1985). Thiopyranose-type heterocycles are exclusively lithiated in the 2-position to provide compounds **66**, which in turn are then reacted with electrophiles **L17** to produce derivatives **69** (Benkeser, R. A. *et al.*, *J. Amer. Chem. Soc.* 1948, 70, 1780; Ramanathan, V. *et al.*, *J. Amer. Chem. Soc.* 1962, 27, 1216; Chadwick, D. J. *et al.*, *J. Chem. Soc. Perkin 1* 1977, 887; Feringa, B. L. *et al.*, *Synthesis* 1988, 316, all of which citations are incorporated herein by reference). Lithiation to the literature methods, by reacting the heterocycles with alkyl-lithium derivatives such as methyl-lithium, *n*-, *s*-, or *t*-butyl-lithium in solvents such as ether, glyme or tetrahydrofuran, preferably ether. Preferably, ligands, such as TMEDA, DMPU or HMPA or another strong base, such as potassium *t*-butoxide are included in the reaction medium. Preferably, the reaction temperature is between -40°C to $+60^{\circ}\text{C}$, and the reaction time is about 1 to 5 hr. The heterocycles are available commercially or prepared by well-known synthetic methods. Next, in a similar fashion, **70** is condensed with **69** to give **III**, wherein each ring has two double bonds. The reactions are performed under similar conditions for substituted heterocycles (for a review on lithiation of 2-substituted furans and thiophenes see *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, W. C. Eds.;

Pergamon Press: Oxford, 1986; Vol.3, p 771). After the formation of the metallated heterocycles, they are *in situ* reacted with electrophiles (*e.g.*, **70**) at temperatures between – 40 °C to +60 °C, for a reaction time of 1 hr to 5 days. The ring double bonds can be selectively reduced or otherwise manipulated by well known synthetic methods to give compounds **IIIa** having only one selectively-placed double bond (*i.e.*, the double bond can be positioned in the desired location within the ring), for example, the methods disclosed in March, J. *Advanced Organic Chemistry; Reactions Mechanisms, and Structure*, 4th ed., 1992, pp. 771-780, incorporated herein by reference.

4.3 Therapeutic Uses of Compounds or Compositions of the Invention

In accordance with the invention, a compound of the invention or a composition of the invention, comprising a compound of the invention and a pharmaceutically acceptable vehicle, is administered to a patient, preferably a human, with or at risk of aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (*e.g.*, Syndrome X), a thrombotic disorder, gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (*e.g.*, Crohn's Disease, ulcerative colitis), arthritis (*e.g.*, rheumatoid arthritis, osteoarthritis), autoimmune disease (*e.g.*, systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism.

In one embodiment, "treatment" or "treating" refers to an amelioration of a disease or disorder, or at least one discernible symptom thereof. In another embodiment, "treatment" or "treating" refers to inhibiting the progression of a disease or disorder, either physically, *e.g.*, stabilization of a discernible symptom, physiologically, *e.g.*, stabilization of a physical parameter, or both.

In certain embodiments, the compounds of the invention or the compositions of the invention are administered to a patient, preferably a human, as a preventative measure against such diseases. As used herein, "prevention" or "preventing" refers to a reduction of the risk of acquiring a given disease or disorder. In a preferred mode of the embodiment, the compositions of the present invention are administered as a preventative measure to a

patient, preferably a human having a genetic predisposition to a aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (e.g., Syndrome X), a thrombotic disorder, inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis), arthritis (e.g., rheumatoid arthritis, osteoarthritis), autoimmune disease (e.g., systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism. Examples of such genetic predispositions include but are not limited to the ϵ 4 allele of apolipoprotein E, which increases the likelihood of Alzheimer's Disease; a loss of function or null mutation in the lipoprotein lipase gene coding region or promoter (e.g., mutations in the coding regions resulting in the substitutions D9N and N291S; for a review of genetic mutations in the lipoprotein lipase gene that increase the risk of cardiovascular diseases, dyslipidemias and dyslipoproteinemias, see Hayden and Ma, 1992, Mol. Cell Biochem. 113:171-176); and familial combined hyperlipidemia and familial hypercholesterolemia .

In another preferred mode of the embodiment, the compounds of the invention or compositions of the invention are administered as a preventative measure to a patient having a non-genetic predisposition to a aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, enhancing bile production, enhancing reverse lipid transport, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (e.g., Syndrome X), a thrombotic disorder, inflammatory processes and diseases like gastrointestinal disease, irritable bowel syndrome (IBS), inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis), arthritis (e.g., rheumatoid arthritis, osteoarthritis), autoimmune disease (e.g., systemic lupus erythematosus), scleroderma, ankylosing

spondylitis, gout and pseudogout, muscle pain: polymyositis/polymyalgia
rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis,
bursitis and other soft tissue rheumatism.. Examples of such non-genetic predispositions
include but are not limited to cardiac bypass surgery and percutaneous transluminal
5 coronary angioplasty, which often lead to restenosis, an accelerated form of atherosclerosis;
diabetes in women, which often leads to polycystic ovarian disease; and cardiovascular
disease, which often leads to impotence. Accordingly, the compositions of the invention
may be used for the prevention of one disease or disorder and concurrently treating another
(e.g., prevention of polycystic ovarian disease while treating diabetes; prevention of
10 impotence while treating a cardiovascular disease).

4.3.1 Treatment of Cardiovascular Diseases

The present invention provides methods for the treatment or prevention of a
cardiovascular disease, comprising administering to a patient a therapeutically effective
amount of a compound or a composition comprising a compound of the invention and a
15 pharmaceutically acceptable vehicle. As used herein, the term "cardiovascular diseases"
refers to diseases of the heart and circulatory system. These diseases are often associated
with dyslipoproteinemias and/or dyslipidemias. Cardiovascular diseases which the
compositions of the present invention are useful for preventing or treating include but are
not limited to arteriosclerosis; atherosclerosis; stroke; ischemia; endothelium dysfunctions,
20 in particular those dysfunctions affecting blood vessel elasticity; peripheral vascular
disease; coronary heart disease; myocardial infarction; cerebral infarction and restenosis.

4.3.2 Treatment of Dyslipidemias

The present invention provides methods for the treatment or prevention of a
dyslipidemia comprising administering to a patient a therapeutically effective amount of a
25 compound or a composition comprising a compound of the invention and a
pharmaceutically acceptable vehicle.

As used herein, the term "dyslipidemias" refers to disorders that lead to or are
manifested by aberrant levels of circulating lipids. To the extent that levels of lipids in the
blood are too high, the compositions of the invention are administered to a patient to restore
30 normal levels. Normal levels of lipids are reported in medical treatises known to those of
skill in the art. For example, recommended blood levels of LDL, HDL, free triglycerides
and others parameters relating to lipid metabolism can be found at the web site of the
American Heart Association and that of the National Cholesterol Education Program of the

National Heart, Lung and Blood Institute (http://www.americanheart.org/cholesterol/about_level.html and http://www.nhlbi.nih.gov/health/public/heart/cho/hbc_what.html, respectively). At the present time, the recommended level of HDL cholesterol in the blood is above 35 mg/dL; the recommended level of LDL cholesterol in the blood is below 130 mg/dL; the recommended LDL:HDL cholesterol ratio in the blood is below 5:1, ideally 3.5:1; and the recommended level of free triglycerides in the blood is less than 200 mg/dL.

Dyslipidemias which the compositions of the present invention are useful for preventing or treating include but are not limited to hyperlipidemia and low blood levels of high density lipoprotein (HDL) cholesterol. In certain embodiments, the hyperlipidemia for prevention or treatment by the compounds of the present invention is familial hypercholesterolemia; familial combined hyperlipidemia; reduced or deficient lipoprotein lipase levels or activity, including reductions or deficiencies resulting from lipoprotein lipase mutations; hypertriglyceridemia; hypercholesterolemia; high blood levels of urea bodies (e.g. β -OH butyric acid); high blood levels of Lp(a) cholesterol; high blood levels of low density lipoprotein (LDL) cholesterol; high blood levels of very low density lipoprotein (VLDL) cholesterol and high blood levels of non-esterified fatty acids.

The present invention further provides methods for altering lipid metabolism in a patient, e.g., reducing LDL in the blood of a patient, reducing free triglycerides in the blood of a patient, increasing the ratio of HDL to LDL in the blood of a patient, and inhibiting saponified and/or non-saponified fatty acid synthesis, said methods comprising administering to the patient a compound or a composition comprising a compound of the invention in an amount effective alter lipid metabolism.

4.3.3 Treatment of Dyslipoproteinemias

The present invention provides methods for the treatment or prevention of a dyslipoproteinemia comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle.

As used herein, the term "dyslipoproteinemias" refers to disorders that lead to or are manifested by aberrant levels of circulating lipoproteins. To the extent that levels of lipoproteins in the blood are too high, the compositions of the invention are administered to a patient to restore normal levels. Conversely, to the extent that levels of lipoproteins in the blood are too low, the compositions of the invention are administered to a patient to restore normal levels. Normal levels of lipoproteins are reported in medical treatises known to those of skill in the art.

Dyslipoproteinemias which the compositions of the present invention are useful for preventing or treating include but are not limited to high blood levels of LDL; high blood levels of apolipoprotein B (apo B); high blood levels of Lp(a); high blood levels of apo(a); high blood levels of VLDL; low blood levels of HDL; reduced or deficient lipoprotein lipase levels or activity, including reductions or deficiencies resulting from lipoprotein lipase mutations; hypoalphalipoproteinemia; lipoprotein abnormalities associated with diabetes; lipoprotein abnormalities associated with obesity; lipoprotein abnormalities associated with Alzheimer's Disease; and familial combined hyperlipidemia.

The present invention further provides methods for reducing apo C-II levels in the blood of a patient; reducing apo C-III levels in the blood of a patient; elevating the levels of HDL associated proteins, including but not limited to apo A-I, apo A-II, apo A-IV and apo E in the blood of a patient; elevating the levels of apo E in the blood of a patient, and promoting clearance of triglycerides from the blood of a patient, said methods comprising administering to the patient a compound or a composition comprising a compound of the invention in an amount effective to bring about said reduction, elevation or promotion, respectively.

4.3.4 Treatment of Glucose Metabolism Disorders

The present invention provides methods for the treatment or prevention of a glucose metabolism disorder, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. As used herein, the term "glucose metabolism disorders" refers to disorders that lead to or are manifested by aberrant glucose storage and/or utilization. To the extent that indicia of glucose metabolism (i.e., blood insulin, blood glucose) are too high, the compositions of the invention are administered to a patient to restore normal levels. Conversely, to the extent that indicia of glucose metabolism are too low, the compositions of the invention are administered to a patient to restore normal levels. Normal indicia of glucose metabolism are reported in medical treatises known to those of skill in the art.

Glucose metabolism disorders which the compositions of the present invention are useful for preventing or treating include but are not limited to impaired glucose tolerance; insulin resistance; insulin resistance related breast, colon or prostate cancer; diabetes, including but not limited to non-insulin dependent diabetes mellitus (NIDDM), insulin dependent diabetes mellitus (IDDM), gestational diabetes mellitus (GDM), and maturity

onset diabetes of the young (MODY); pancreatitis; hypertension; polycystic ovarian disease; and high levels of blood insulin and/or glucose.

The present invention further provides methods for altering glucose metabolism in a patient, for example to increase insulin sensitivity and/or oxygen consumption of a patient, said methods comprising administering to the patient a compound or a composition comprising a compound of the invention in an amount effective to alter glucose metabolism.

4.3.5 Treatment of PPAR-Associated Disorders

The present invention provides methods for the treatment or prevention of a PPAR-associated disorder, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. As used herein, "treatment or prevention of PPAR associated disorders" encompasses treatment or prevention of rheumatoid arthritis; multiple sclerosis; psoriasis; inflammatory bowel diseases; breast; colon or prostate cancer; low levels of blood HDL; low levels of blood, lymph and/or cerebrospinal fluid apo E; low blood, lymph and/or cerebrospinal fluid levels of apo A-I; high levels of blood VLDL; high levels of blood LDL; high levels of blood triglyceride; high levels of blood apo B; high levels of blood apo C-III and reduced ratio of post-heparin hepatic lipase to lipoprotein lipase activity. HDL may be elevated in lymph and/or cerebral fluid.

4.3.6 Treatment of Renal Diseases

The present invention provides methods for the treatment or prevention of a renal disease, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. Renal diseases that can be treated by the compounds of the present invention include glomerular diseases (including but not limited to acute and chronic glomerulonephritis, rapidly progressive glomerulonephritis, nephrotic syndrome, focal proliferative glomerulonephritis, glomerular lesions associated with systemic disease, such as systemic lupus erythematosus, Goodpasture's syndrome, multiple myeloma, diabetes, neoplasia, sickle cell disease, and chronic inflammatory diseases), tubular diseases (including but not limited to acute tubular necrosis and acute renal failure, polycystic renal diseasemedullary sponge kidney, medullary cystic disease, nephrogenic diabetes, and renal tubular acidosis), tubulointerstitial diseases (including but not limited to pyelonephritis, drug and toxin induced tubulointerstitial nephritis, hypercalcemic nephropathy, and

hypokalemic nephropathy) acute and rapidly progressive renal failure, chronic renal failure, nephrolithiasis, or tumors (including but not limited to renal cell carcinoma and nephroblastoma). In a most preferred embodiment, renal diseases that are treated by the compounds of the present invention are vascular diseases, including but not limited to
5 hypertension, nephrosclerosis, microangiopathic hemolytic anemia, atheroembolic renal disease, diffuse cortical necrosis, and renal infarcts.

4.3.7 Treatment of Cancer

The present invention provides methods for the treatment or prevention of cancer, comprising administering to a patient a therapeutically effective amount of a compound or a
10 composition comprising a compound of the invention and a pharmaceutically acceptable vehicle. Types of cancer that can be treated using a Compound of the Invention include, but are not limited to, those listed in Table 2.

TABLE 2

Solid tumors, including but not limited to

fibrosarcoma
myxosarcoma
liposarcoma
chondrosarcoma
osteogenic sarcoma
chordoma
angiosarcoma
endotheliosarcoma
lymphangiosarcoma
lymphangioendotheliosarcoma
synovioma
mesothelioma
Ewing's tumor
leiomyosarcoma
rhabdomyosarcoma
colon cancer
colorectal cancer
kidney cancer

pancreatic cancer
bone cancer
breast cancer
ovarian cancer
prostate cancer
esophageal cancer
stomach cancer
oral cancer
nasal cancer
throat cancer
squamous cell carcinoma
basal cell carcinoma
adenocarcinoma
sweat gland carcinoma
sebaceous gland carcinoma
papillary carcinoma
papillary adenocarcinomas
cystadenocarcinoma
medullary carcinoma
bronchogenic carcinoma
renal cell carcinoma
hepatoma
bile duct carcinoma
choriocarcinoma
seminoma
embryonal carcinoma
Wilms' tumor
cervical cancer
uterine cancer
testicular cancer
small cell lung carcinoma
bladder carcinoma
lung cancer
epithelial carcinoma

glioma
glioblastoma multiforme
astrocytoma
medulloblastoma
craniopharyngioma
ependymoma
pinealoma
hemangioblastoma
acoustic neuroma
oligodendroglioma
meningioma
skin cancer
melanoma
neuroblastoma
retinoblastoma

Blood-borne cancers, including but not limited to:

acute lymphoblastic B-cell leukemia
acute lymphoblastic T-cell leukemia
acute myeloblastic leukemia "AML"
acute promyelocytic leukemia "APL"
acute monoblastic leukemia
acute erythroleukemic leukemia
acute megakaryoblastic leukemia
acute myelomonocytic leukemia
acute nonlymphocytic leukemia
acute undifferentiated leukemia
chronic myelocytic leukemia "CML"
chronic lymphocytic leukemia "CLL"
hairy cell leukemia
multiple myeloma

Acute and chronic leukemias

Lymphoblastic
myelogenous
lymphocytic

myelocytic leukemias

Lymphomas:

Hodgkin's disease

non-Hodgkin's Lymphoma

Multiple myeloma

Waldenström's macroglobulinemia

Heavy chain disease

Polycythemia vera

Cancer, including, but not limited to, a tumor, metastasis, or any disease or disorder characterized by uncontrolled cell growth, can be treated or prevented by administration of a Compound of the Invention.

5 **4.3.8 Treatment of Other Diseases**

The present invention provides methods for the treatment or prevention of Alzheimer's Disease, Syndrome X, septicemia, thrombotic disorders, obesity, pancreatitis, hypertension, inflammation, and impotence, comprising administering to a patient a therapeutically effective amount of a compound or a composition comprising a compound
10 of the invention and a pharmaceutically acceptable vehicle.

As used herein, "treatment or prevention of Alzheimer's Disease" encompasses treatment or prevention of lipoprotein abnormalities associated with Alzheimer's Disease.

As used herein, "treatment or prevention of Syndrome X or Metabolic Syndrome" encompasses treatment or prevention of a symptom thereof, including but not limited to
15 impaired glucose tolerance, hypertension and dyslipidemia/dyslipoproteinemia.

As used herein, "treatment or prevention of septicemia" encompasses treatment or prevention of septic shock.

As used herein, "treatment or prevention of thrombotic disorders" encompasses treatment or prevention of high blood levels of fibrinogen and promotion of fibrinolysis.

20 In addition to treating or preventing obesity, the compositions of the invention can be administered to an individual to promote weight reduction of the individual.

As used herein, "treatment or prevention of diabetic nephropathy" encompasses treating or preventing kidney disease that develops as a result of diabetes mellitus (DM). Diabetes mellitus is a disorder in which the body is unable to metabolize carbohydrates
25 (e.g., food starches, sugars, cellulose) properly. The disease is characterized by excessive amounts of sugar in the blood (hyperglycemia) and urine; inadequate production and/or

utilization of insulin; and by thirst, hunger, and loss of weight. Thus, the compounds of the invention can also be used to treat or prevent diabetes mellitus.

As used herein, “treatment or prevention of diabetic retinopathy” encompasses treating or preventing complications of diabetes that lead to or cause blindness. Diabetic retinopathy occurs when diabetes damages the tiny blood vessels inside the retina, the light-sensitive tissue at the back of the eye.

As used herein, “treatment or prevention of impotence” includes treating or preventing erectile dysfunction, which encompasses the repeated inability to get or keep an erection firm enough for sexual intercourse. The word “impotence” may also be used to describe other problems that interfere with sexual intercourse and reproduction, such as lack of sexual desire and problems with ejaculation or orgasm. The term “treatment or prevention of impotence includes, but is not limited to impotence that results as a result of damage to nerves, arteries, smooth muscles, and fibrous tissues, or as a result of disease, such as, but not limited to, diabetes, kidney disease, chronic alcoholism, multiple sclerosis, atherosclerosis, vascular disease, and neurologic disease.

As used herein, “treatment or prevention of hypertension” encompasses treating or preventing blood flow through the vessels at a greater than normal force, which strains the heart; harms the arteries; and increases the risk of heart attack, stroke, and kidney problems. The term hypertension includes, but is not limited to, cardiovascular disease, essential hypertension, hyperpiesia, hyperpiesis, malignant hypertension, secondary hypertension, or white-coat hypertension.

As used herein, “treatment or prevention of inflammation” encompasses treating or preventing inflammation diseases including, but not limited to, chronic inflammatory disorders of the joints including arthritis, e.g., rheumatoid arthritis and osteoarthritis; respiratory distress syndrome, inflammatory bowel diseases such as ileitis, ulcerative colitis and Crohn’s disease; and inflammatory lung disorders such as asthma and chronic obstructive airway disease, inflammatory disorders of the eye such as corneal dystrophy, trachoma, onchocerciasis, uveitis, sympathetic ophthalmitis, and endophthalmitis; inflammatory disorders of the gum, e.g., periodontitis and gingivitis; tuberculosis; leprosy; inflammatory diseases of the kidney including glomerulonephritis and nephrosis; inflammatory disorders of the skin including acne, sclerodermatitis, psoriasis, eczema, photoaging and wrinkles; inflammatory diseases of the central nervous system, including AIDS-related neurodegeneration, stroke, neurotrauma, Alzheimer’s disease, encephalomyelitis and viral or autoimmune encephalitis; autoimmune diseases including

immune-complex vasculitis, systemic lupus and erythematoses; systemic lupus erythematosus (SLE); and inflammatory diseases of the heart such as cardiomyopathy.

4.4 Combination Therapy

5 In certain embodiments of the present invention, the compounds and compositions of the invention can be used in combination therapy with at least one other therapeutic agent. The compound of the invention and the therapeutic agent can act additively or, more preferably, synergistically. In a preferred embodiment, a compound or a composition comprising a compound of the invention is administered concurrently with the
10 administration of another therapeutic agent, which can be part of the same composition as the compound of the invention or a different composition. In another embodiment, a compound or a composition comprising a compound of the invention is administered prior or subsequent to administration of another therapeutic agent. As many of the disorders for which the compounds and compositions of the invention are useful in treating are chronic
15 disorders, in one embodiment combination therapy involves alternating between administering a compound or a composition comprising a compound of the invention and a composition comprising another therapeutic agent, e.g., to minimize the toxicity associated with a particular drug. The duration of administration of each drug or therapeutic agent can be, e.g., one month, three months, six months, or a year. In certain embodiments, when a
20 composition of the invention is administered concurrently with another therapeutic agent that potentially produces adverse side effects including but not limited to toxicity, the therapeutic agent can advantageously be administered at a dose that falls below the threshold at which the adverse side is elicited.

 The present compositions can be administered together with a statin. Statins for use
25 in combination with the compounds and compositions of the invention include but are not limited to atorvastatin, pravastatin, fluvastatin, lovastatin, simvastatin, and cerivastatin.

 The present compositions can also be administered together with a PPAR agonist, for example a thiazolidinedione or a fibrate. Thiazolidinediones for use in combination with the compounds and compositions of the invention include but are not limited to 5 ((4
30 (2 (methyl 2 pyridinylamino)ethoxy)phenyl)methyl) 2,4 thiazolidinedione, troglitazone, pioglitazone, ciglitazone, WAY 120,744, englitazone, AD 5075, darglitazone, and rosiglitazone. Fibrates for use in combination with the compounds and compositions of the invention include but are not limited to gemfibrozil, fenofibrate, clofibrate, or ciprofibrate. As mentioned previously, a therapeutically effective amount of a fibrate or

thiazolidinedione often has toxic side effects. Accordingly, in a preferred embodiment of the present invention, when a composition of the invention is administered in combination with a PPAR agonist, the dosage of the PPAR agonist is below that which is accompanied by toxic side effects.

5 The present compositions can also be administered together with a bile acid binding resin. Bile acid binding resins for use in combination with the compounds and compositions of the invention include but are not limited to cholestyramine and colestipol hydrochloride. The present compositions can also be administered together with niacin or nicotinic acid. The present compositions can also be administered together with a RXR
10 agonist. RXR agonists for use in combination with the compounds of the invention include but are not limited to LG 100268, LGD 1069, 9-cis retinoic acid, 2 (1 (3,5,5,8,8 pentamethyl 5,6,7,8 tetrahydro 2 naphthyl) cyclopropyl) pyridine 5 carboxylic acid, or 4 ((3,5,5,8,8 pentamethyl 5,6,7,8 tetrahydro 2 naphthyl)2 carbonyl) benzoic acid. The present compositions can also be administered together with an anti-obesity drug. Anti-obesity
15 drugs for use in combination with the compounds of the invention include but are not limited to β -adrenergic receptor agonists, preferably β -3 receptor agonists, fenfluramine, dexfenfluramine, sibutramine, bupropion, fluoxetine, and phentermine. The present compositions can also be administered together with a hormone. Hormones for use in combination with the compounds of the invention include but are not limited to thyroid
20 hormone, estrogen and insulin. Preferred insulins include but are not limited to injectable insulin, transdermal insulin, inhaled insulin, or any combination thereof. As an alternative to insulin, an insulin derivative, secretagogue, sensitizer or mimetic may be used. Insulin secretagogues for use in combination with the compounds of the invention include but are not limited to forskolin, dibutryl cAMP or isobutylmethylxanthine (IBMX).

25 The present compositions can also be administered together with a phosphodiesterase type 5 ("PDE5") inhibitor to treat or prevent disorders, such as but not limited to, impotence. In a particular, embodiment the combination is a synergistic combination of a composition of the invention and a PDE5 inhibitor.

 The present compositions can also be administered together with a tyrophostine or
30 an analog thereof. Tyrophostines for use in combination with the compounds of the invention include but are not limited to tyrophostine 51.

 The present compositions can also be administered together with sulfonylurea-based drugs. Sulfonylurea-based drugs for use in combination with the compounds of the invention include, but are not limited to, glisoxepid, glyburide, acetohexamide,

chlorpropamide, glibornuride, tolbutamide, tolazamide, glipizide, gliclazide, gliquidone, glyhexamide, phenbutamide, and tolcyclamide. The present compositions can also be administered together with a biguanide. Biguanides for use in combination with the compounds of the invention include but are not limited to metformin, phenformin and
5 buformin.

The present compositions can also be administered together with an α -glucosidase inhibitor. α -glucosidase inhibitors for use in combination with the compounds of the invention include but are not limited to acarbose and miglitol.

The present compositions can also be administered together with an apo A-I agonist.
10 In one embodiment, the apo A-I agonist is the Milano form of apo A-I (apo A-IM). In a preferred mode of the embodiment, the apo A-IM for administration in conjunction with the compounds of the invention is produced by the method of U.S. Patent No. 5,721,114 to Abrahamsen. In a more preferred embodiment, the apo A-I agonist is a peptide agonist. In a preferred mode of the embodiment, the apo A-I peptide agonist for administration in
15 conjunction with the compounds of the invention is a peptide of U.S. Patent No. 6,004,925 or 6,037,323 to Dasseux.

The present compositions can also be administered together with apolipoprotein E (apo E). In a preferred mode of the embodiment, the apoE for administration in conjunction with the compounds of the invention is produced by the method of U.S. Patent No.
20 5,834,596 to Ageland.

In yet other embodiments, the present compositions can be administered together with an HDL-raising drug; an HDL enhancer; or a regulator of the apolipoprotein A-I, apolipoprotein A-IV and/or apolipoprotein genes.

In one embodiment, the other therapeutic agent can be an antiemetic agent. Suitable
25 antiemetic agents include, but are not limited to, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acethylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl,
30 pipamazine, scopolamine, sulphiride, tetrahydrocannabinols, thiethylperazine, thioproperazine and tropisetron.

In another embodiment, the other therapeutic agent can be an hematopoietic colony stimulating factor. Suitable hematopoietic colony stimulating factors include, but are not limited to, filgrastim, sargramostim, molgramostim and erythropoietin alfa.

In still another embodiment, the other therapeutic agent can be an opioid or non-opioid analgesic agent. Suitable opioid analgesic agents include, but are not limited to, morphine, heroin, hydromorphone, hydrocodone, oxymorphone, oxycodone, metopon, apomorphine, normorphine, etorphine, buprenorphine, meperidine, lopermide, anileridine, ethoheptazine, piminidine, betaprodine, diphenoxylate, fentanil, sufentanil, alfentanil, remifentanil, levorphanol, dextromethorphan, phenazocine, pentazocine, cyclazocine, methadone, isomethadone and propoxyphene. Suitable non-opioid analgesic agents include, but are not limited to, aspirin, celecoxib, rofecoxib, diclofinac, diflusal, etodolac, fenoprofen, flurbiprofen, ibuprofen, ketoprofen, indomethacin, ketorolac, meclofenamate, mefanamic acid, nabumetone, naproxen, piroxicam and sulindac.

4.4.1 Combination Therapy of Cardiovascular Diseases

The present compositions can be administered together with a known cardiovascular drug. Cardiovascular drugs for use in combination with the compounds of the invention to prevent or treat cardiovascular diseases include but are not limited to peripheral antiadrenergic drugs, centrally acting antihypertensive drugs (e.g., methyldopa, methyldopa HCl), antihypertensive direct vasodilators (e.g., diazoxide, hydralazine HCl), drugs affecting renin-angiotensin system, peripheral vasodilators, phentolamine, antianginal drugs, cardiac glycosides, inodilators (e.g., amrinone, milrinone, enoximone, fenoximone, imazodan, sulmazole), antidysrhythmic drugs, calcium entry blockers, ranitine, bosentan, and rezulin.

4.4.2 Combination Therapy of Cancer

The present invention includes methods for treating cancer, comprising administering to an animal in need thereof an effective amount of a Compound of the Invention and another therapeutic agent that is an anti-cancer agent. Suitable anticancer agents include, but are not limited to, those listed in Table 3.

TABLE 3

Alkylating agents

Nitrogen mustards:

Cyclophosphamide

Ifosfamide

trofosfamide

	Chlorambucil	
	Treos	
Nitrosoureas:	carbustine (BCNU)	
	Lomustine (CCNU)	
Alkylsulphonates	Busulfan	
	Treosulfan	
Triazenes:	Dacarbazine	
Platinum containing compounds:	Cisplatin	
	carboplatin	
<u>Plant Alkaloids</u>		
Vinca alkaloids:	Vicristine	
	Vinblastine	
	Vindesine	
	Vinorelbine	
Taxoids:	paclitaxel	
	Docetaxol	
<u>DNA Topoisomerase Inhibitors</u>		
Epipodophyllins:	Etoposide	
	Teniposide	
	Topotecan	
	9-aminocamptothecin	
	camptothecin	
	crisnatol	
<u>mitomycins:</u>	Mitomycin C	
Anti-metabolites		
<u>Anti-folates:</u>		
DHFR inhibitors:	METHOTREXATE	
	Trimetrexate	
IMP dehydrogenase Inhibitors:	Mycophenolic	acid
	Tiazofurin	
	Ribavirin	
	EICAR	
Ribonucleotide reductase Inhibitors:	Hydroxyurea	

	deferoxamine
<u>Pyrimidine analogs:</u>	
Uracil analogs	5-Fluorouracil
	Floxuridine
	Doxifluridine
	Ratitrexed
Cytosine analogs	cytarabine (ara C)
	Cytosine arabinoside
	fludarabine
<u>Purine analogs:</u>	mercaptopurine
	Thioguanine
<u>Hormonal therapies:</u>	
Receptor antagonists:	
Anti-estrogen	Tamoxifen
	Raloxifene
	megestrol
	goserelin
	Leuprolide acetate
LHRH agonists:	flutamide
	bicalutamide
<u>Retinoids/Deletoids</u>	
<u>Vitamin D3 analogs:</u>	EB 1089
	CB 1093
	KH 1060
<u>Photodynamic therapies:</u>	verteporfin (BPD-MA)
	Phthalocyanine
	photosensitizer Pc4
	Demethoxy-hypocrellin A
	(2BA-2-DMHA)
<u>Cytokines:</u>	Interferon- α
	Interferon- γ
	Tumor necrosis factor
<u>Others:</u>	
Isoprenylation inhibitors:	Lovastatin

Dopaminergic neurotoxins:	1-methyl-4-phenylpyridinium ion
Cell cycle inhibitors:	staurosporine
Actinomycines:	Actinomycin D
	Dactinomycin
Bleomycins:	bleomycin A2
	Bleomycin B2
	Peplomycin
Anthracyclines:	daunorubicin
	Doxorubicin (adriamycin)
	Idarubicin
	Epirubicin
	Pirarubicin
	Zorubicin
	Mitoxantrone
MDR inhibitors	verapamil
Ca ²⁺ ATPase inhibitors:	thapsigargin

In a specific embodiment, a composition of the invention further comprises one or more chemotherapeutic agents and/or is administered concurrently with radiation therapy. In another specific embodiment, chemotherapy or radiation therapy is administered prior or subsequent to administration of a present composition, preferably at least an hour, five hours, 12 hours, a day, a week, a month, more preferably several months (e.g., up to three months), subsequent to administration of a composition of the invention.

In other embodiments, the invention provides methods for treating or preventing cancer, comprising administering to an animal in need thereof an effective amount of a Compound of the Invention and a chemotherapeutic agent. In one embodiment the chemotherapeutic agent is that with which treatment of the cancer has not been found to be refractory. In another embodiment, the chemotherapeutic agent is that with which the treatment of cancer has been found to be refractory. The Compounds of the Invention can be administered to an animal that has also undergone surgery as treatment for the cancer.

In one embodiment, the additional method of treatment is radiation therapy.

In a specific embodiment, the Compound of the Invention is administered concurrently with the chemotherapeutic agent or with radiation therapy. In another specific embodiment, the chemotherapeutic agent or radiation therapy is administered prior or

subsequent to administration of a Compound of the Invention, preferably at least an hour, five hours, 12 hours, a day, a week, a month, more preferably several months (e.g., up to three months), prior or subsequent to administration of a Compound of the Invention.

A chemotherapeutic agent can be administered over a series of sessions, any one or a combination of the chemotherapeutic agents listed in Table 3 can be administered. With respect to radiation, any radiation therapy protocol can be used depending upon the type of cancer to be treated. For example, but not by way of limitation, x-ray radiation can be administered; in particular, high-energy megavoltage (radiation of greater than 1 MeV energy) can be used for deep tumors, and electron beam and orthovoltage x-ray radiation can be used for skin cancers. Gamma-ray emitting radioisotopes, such as radioactive isotopes of radium, cobalt and other elements, can also be administered.

Additionally, the invention provides methods of treatment of cancer with a Compound of the Invention as an alternative to chemotherapy or radiation therapy where the chemotherapy or the radiation therapy has proven or can prove too toxic, e.g., results in unacceptable or unbearable side effects, for the subject being treated. The animal being treated can, optionally, be treated with another cancer treatment such as surgery, radiation therapy or chemotherapy, depending on which treatment is found to be acceptable or bearable.

The Compounds of the Invention can also be used in an in vitro or ex vivo fashion, such as for the treatment of certain cancers, including, but not limited to leukemias and lymphomas, such treatment involving autologous stem cell transplants. This can involve a multi-step process in which the animal's autologous hematopoietic stem cells are harvested and purged of all cancer cells, the patient's remaining bone-marrow cell population is then eradicated via the administration of a high dose of a Compound of the Invention with or without accompanying high dose radiation therapy, and the stem cell graft is infused back into the animal. Supportive care is then provided while bone marrow function is restored and the animal recovers.

4.5 Surgical Uses

Cardiovascular diseases such as atherosclerosis often require surgical procedures such as angioplasty. Angioplasty is often accompanied by the placement of a reinforcing a metallic tube shaped structure known as a "stent" into a damaged coronary artery. For more serious conditions, open heart surgery such as coronary bypass surgery may be required. These surgical procedures entail using invasive surgical devices and/or implants, and are associated with a high risk of restenosis and thrombosis. Accordingly, the compounds and

compositions of the invention may be used as coatings on surgical devices (e.g., catheters) and implants (e.g., stents) to reduce the risk of restenosis and thrombosis associated with invasive procedures used in the treatment of cardiovascular diseases.

4.6 Veterinary and Livestock Uses

5 A composition of the invention can be administered to a non-human animal for a veterinary use for treating or preventing a disease or disorder disclosed herein.

In a specific embodiment, the non-human animal is a household pet. In another specific embodiment, the non-human animal is a livestock animal. In a preferred embodiment, the non-human animal is a mammal, most preferably a cow, horse, sheep, pig, 10 cat, dog, mouse, rat, rabbit, or guinea pig. In another preferred embodiment, the non-human animal is a fowl species, most preferably a chicken, turkey, duck, goose, or quail.

In addition to veterinary uses, the compounds and compositions of the invention can be used to reduce the fat content of livestock to produce leaner meats. Alternatively, the compounds and compositions of the invention can be used to reduce the cholesterol content 15 of eggs by administering the compounds to a chicken, quail, or duck hen. For non-human animal uses, the compounds and compositions of the invention can be administered via the animals' feed or orally as a drench composition.

4.7 Therapeutic/Prophylactic Administration and Compositions

Due to the activity of the compounds and compositions of the invention, they are 20 useful in veterinary and human medicine. As described above, the compounds and compositions of the invention are useful for the treatment or prevention of aging, Alzheimer's Disease, cancer, cardiovascular disease, diabetic nephropathy, diabetic retinopathy, a disorder of glucose metabolism, dyslipidemia, dyslipoproteinemia, hypertension, impotence, inflammation, insulin resistance, lipid elimination in bile, 25 modulating C reactive protein, obesity, oxysterol elimination in bile, pancreatitis, Parkinson's disease, a peroxisome proliferator activated receptor-associated disorder, phospholipid elimination in bile, renal disease, septicemia, metabolic syndrome disorders (e.g., Syndrome X), a thrombotic disorder, enhancing bile production, enhancing reverse lipid transport, inflammatory processes and diseases like gastrointestinal disease, irritable 30 bowel syndrome (IBS), inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis), arthritis (e.g., rheumatoid arthritis, osteoarthritis), autoimmune disease (e.g., systemic lupus erythematosus), scleroderma, ankylosing spondylitis, gout and pseudogout,

muscle pain: polymyositis/polymyalgia rheumatica/fibrositis; infection and arthritis, juvenile rheumatoid arthritis, tendonitis, bursitis and other soft tissue rheumatism.

The invention provides methods of treatment and prophylaxis by administration to a patient of a therapeutically effective amount of a compound or a composition comprising a compound of the invention. The patient is an animal, including, but not limited, to an animal such a cow, horse, sheep, pig, chicken, turkey, quail, cat, dog, mouse, rat, rabbit, guinea pig, etc., and is more preferably a mammal, and most preferably a human.

The compounds and compositions of the invention, are preferably administered orally. The compounds and compositions of the invention may also be administered by any other convenient route, for example, by intravenous infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with another biologically active agent. Administration can be systemic or local. Various delivery systems are known, e.g., encapsulation in liposomes, microparticles, microcapsules, capsules, etc., and can be used to administer a compound of the invention. In certain embodiments, more than one compound of the invention is administered to a patient. Methods of administration include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intravaginal, transdermal, rectally, by inhalation, or topically, particularly to the ears, nose, eyes, or skin. The preferred mode of administration is left to the discretion of the practitioner, and will depend in-part upon the site of the medical condition. In most instances, administration will result in the release of the compounds of the invention into the bloodstream.

In specific embodiments, it may be desirable to administer one or more compounds of the invention locally to the area in need of treatment. This may be achieved, for example, and not by way of limitation, by local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of an atherosclerotic plaque tissue.

In certain embodiments, for example, for the treatment of Alzheimer's Disease, it may be desirable to introduce one or more compounds of the invention into the central nervous system by any suitable route, including intraventricular, intrathecal and epidural

injection. Intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir.

Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent, or via perfusion in a fluorocarbon or synthetic pulmonary surfactant. In certain embodiments, the compounds of the invention can be formulated as a suppository, with traditional binders and vehicles such as triglycerides.

In another embodiment, the compounds and compositions of the invention can be delivered in a vesicle, in particular a liposome (see Langer, 1990, *Science* 249:1527 1533; Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353 365 (1989); Lopez Berestein, *ibid.*, pp. 317 327; see generally *ibid.*).

In yet another embodiment, the compounds and compositions of the invention can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201; Buchwald et al., 1980, *Surgery* 88:507 Saudek et al., 1989, *N. Engl. J. Med.* 321:574). In another embodiment, polymeric materials can be used (see *Medical Applications of Controlled Release*, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, 1983, *J. Macromol. Sci. Rev. Macromol. Chem.* 23:61; see also Levy et al., 1985, *Science* 228:190; During et al., 1989, *Ann. Neurol.* 25:351; Howard et al., 1989, *J. Neurosurg.* 71:105). In yet another embodiment, a controlled-release system can be placed in proximity of the target area to be treated, e.g., the liver, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in *Medical Applications of Controlled Release*, *supra*, vol. 2, pp. 115 138 (1984)). Other controlled-release systems discussed in the review by Langer, 1990, *Science* 249:1527 1533) may be used.

The present compositions will contain a therapeutically effective amount of a compound of the invention, optionally more than one compound of the invention, preferably in purified form, together with a suitable amount of a pharmaceutically acceptable vehicle so as to provide the form for proper administration to the patient.

In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "vehicle" refers to a diluent, adjuvant, excipient, or carrier

with which a compound of the invention is administered. Such pharmaceutical vehicles can be liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. The pharmaceutical vehicles can be saline, gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating and coloring agents may be used. When administered to a patient, the compounds and compositions of the invention and pharmaceutically acceptable vehicles are preferably sterile. Water is a preferred vehicle when the compound of the invention is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid vehicles, particularly for injectable solutions. Suitable pharmaceutical vehicles also include excipients such as starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The present compositions, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents.

The present compositions can take the form of solutions, suspensions, emulsion, tablets, pills, pellets, capsules, capsules containing liquids, powders, sustained-release formulations, suppositories, emulsions, aerosols, sprays, suspensions, or any other form suitable for use. In one embodiment, the pharmaceutically acceptable vehicle is a capsule (see e.g., U.S. Patent No. 5,698,155). Other examples of suitable pharmaceutical vehicles are described in "Remington's Pharmaceutical Sciences" by E.W. Martin.

In a preferred embodiment, the compounds and compositions of the invention are formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compounds and compositions of the invention for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the compositions may also include a solubilizing agent. Compositions for intravenous administration may optionally include a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the compound of the invention is to be administered by intravenous infusion, it can be dispensed, for example, with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the compound of the

invention is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

Compounds and compositions of the invention for oral delivery may be in the form of tablets, lozenges, aqueous or oily suspensions, granules, powders, emulsions, capsules, syrups, or elixirs. Compounds and compositions of the invention for oral delivery can also be formulated in foods and food mixes. Orally administered compositions may contain one or more optionally agents, for example, sweetening agents such as fructose, aspartame or saccharin; flavoring agents such as peppermint, oil of wintergreen, or cherry; coloring agents; and preserving agents, to provide a pharmaceutically palatable preparation.

Moreover, where in tablet or pill form, the compositions may be coated to delay disintegration and absorption in the gastrointestinal tract thereby providing a sustained action over an extended period of time. Selectively permeable membranes surrounding an osmotically active driving compound are also suitable for orally administered compounds and compositions of the invention. In these later platforms, fluid from the environment surrounding the capsule is imbibed by the driving compound, which swells to displace the agent or agent composition through an aperture. These delivery platforms can provide an essentially zero order delivery profile as opposed to the spiked profiles of immediate release formulations. A time delay material such as glycerol monostearate or glycerol stearate may also be used. Oral compositions can include standard vehicles such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Such vehicles are preferably of pharmaceutical grade.

The amount of a compound of the invention that will be effective in the treatment of a particular disorder or condition disclosed herein will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro or in vivo assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the compositions will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for oral administration are generally about 0.001 milligram to 2000 milligrams of a compound of the invention per kilogram body weight. In specific preferred embodiments of the invention, the oral dose is 0.01 milligram to 1000 milligrams per kilogram body weight, more preferably 0.1 milligram to 100 milligrams per kilogram body weight, more preferably 0.5 milligram to 25 milligrams per kilogram body weight, and yet more preferably 1 milligram to 10 milligrams per kilogram body weight. In a most

preferred embodiment, the oral dose is 5 milligrams of a compound of the invention per kilogram body weight. The dosage amounts described herein refer to total amounts administered; that is, if more than one compound of the invention is administered, the preferred dosages correspond to the total amount of the compounds of the invention administered. Oral compositions preferably contain 10% to 95% active ingredient by weight..

Suitable dosage ranges for intravenous (i.v.) administration are 0.01 milligram to 1000 milligrams per kilogram body weight, 0.1 milligram to 350 milligrams per kilogram body weight, and 1 milligram to 100 milligrams per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Suppositories generally contain 0.01 milligram to 50 milligrams of a compound of the invention per kilogram body weight and comprise active ingredient in the range of 0.5% to 10% by weight. Recommended dosages for intradermal, intramuscular, intraperitoneal, subcutaneous, epidural, sublingual, intracerebral, intravaginal, transdermal administration or administration by inhalation are in the range of 0.001 milligram to 200 milligrams per kilogram of body weight. Suitable doses of the compounds of the invention for topical administration are in the range of 0.001 milligram to 1 milligram, depending on the area to which the compound is administered. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems. Such animal models and systems are well known in the art.

The invention also provides pharmaceutical packs or kits comprising one or more containers filled with one or more compounds of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration. In a certain embodiment, the kit contains more than one compound of the invention. In another embodiment, the kit comprises a compound of the invention and another lipid-mediating compound, including but not limited to a statin, a thiazolidinedione, or a fibrate.

The compounds of the invention are preferably assayed in vitro and in vivo, for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays can be used to determine whether administration of a specific compound of the invention or a combination of compounds of the invention is preferred for lowering fatty acid synthesis. The compounds and compositions of the invention may also be demonstrated to be effective and safe using animal model systems.

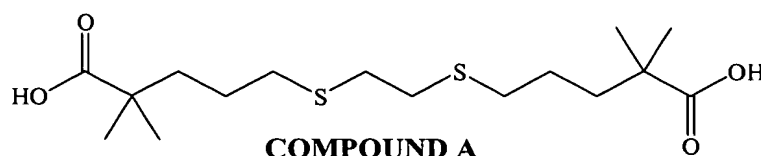
Other methods will be known to the skilled artisan and are within the scope of the invention.

The following examples are provided by way of illustration and not limitation.

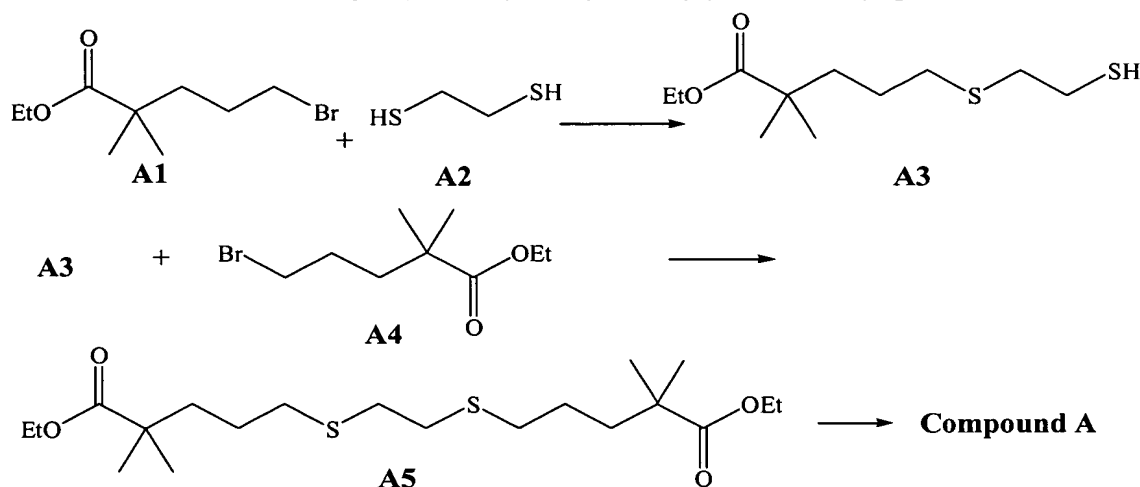
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5. SYNTHETIC EXAMPLES

5.1 Synthesis of 5-[2-(4-Carboxy-4-methyl-pentylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-pentanoic acid (Compound A)



5-[2-(4-Carboxy-4-methyl-pentylsulfanyl)-ethylsulfanyl]-2,2-dimethyl-pentanoic acid



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5-Bromo-2,2-dimethyl-1-pentanol. Under argon, a suspension of LiBH_4 (14.8 g, 646 mmol) in methylene chloride (600 mL) was stirred and methanol (25.6 mL, 20.2 g, 629 mmol) was added dropwise, taking care to keep the temperature below 30 °C. To this mixture, a solution of ethyl 5-bromo-2,2-dimethylpentanoate (100.0 g, 392 mmol; prepared according to Kuwahara *et al. Chem. Pharm. Bull* 1997, 48, 1447) in methylene chloride (200 mL) was added dropwise over 20 minutes, and the solution was heated under reflux for 21 h. After chilling in an ice-bath, the reaction was quenched by adding H_2O dropwise (100 mL). After the effervescence stopped, 2 N HCl (125 mL) was added dropwise and the solution was stirred until the effervescence ceased. The procedure was repeated with another portion of 2 N HCl (125 mL). The layers were separated, and the aqueous layer was extracted with an additional portion of methylene chloride (500 mL). The two organic

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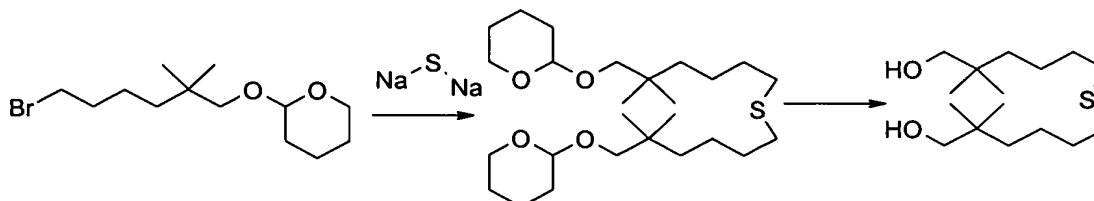
portions were combined and washed with 2 N HCl (300 mL), then sat. NaHCO₃ (300 mL). After drying the organics (Na₂SO₄), the solvent was evaporated to yield the product as a light yellow oil (77.6 g, 91 % yield). ¹H NMR (300 MHz, d₆-DMSO), δ (ppm): 4.42 (s, 1 H); 3.45 (t, 2 H, *J* = 6.6); 3.08 (s, 2 H); 1.84 - 1.69 (m, 2 H); 1.27 (t, 2 H, *J* = 8.3); 0.78 (s, 6 H). ¹³C NMR (75 Mhz, d₆-DMSO), δ (ppm): 69.7, 36.9, 35.7, 34.5, 27.4, 24.0.

5-Bromo-2,2-dimethyl-1-(tetrahydropyranyloxy)-pentane. 5-Bromo-2,2-dimethyl-1-pentanol (77.4 g, 357 mmol) was dissolved in dichloromethane (400 mL), and *p*-toluenesulfonic acid (6.9 g, 36 mmol) was added. The mixture was stirred under argon, chilled in an ice-bath, then was added 3,4-dihydro-2H-pyran (37.2 g, 428 mmol) and stirred, gradually letting warm to rt overnight. The reaction mixture was then filtered through neutral alumina (100 g); the alumina was rinsed with additional dichloromethane (600 mL). After evaporating to about 500 mL, the organic layer was extracted with sat. NaHCO₃ (3 200 mL), then dried over MgSO₄. The solution was concentrated under reduced pressure to produce the expected product (107.83 g, 97 % yield) as a yellow oil. ¹H NMR (300 MHz, CDCl₃), δ (ppm): 4.55 (m, 1 H); 3.83 (m, 1 H); 3.51 (m, 1 H); 3.47 (d, 1 H, *J* = 9.0); 3.38 (t, 2 H, *J* = 6.8); 2.98 (d, 1 H, *J* = 9.0); 1.94 - 1.75 (m, 2 H); 1.75 - 1.44 (m, 6 H); 1.40 (t, 2 H, *J* = 8.5); 0.93-0.87 (m, 6 H). ¹³C NMR (75 MHz, CDCl₃), δ (ppm): 99.0, 76.2, 61.9, 37.9, 34.6, 34.0, 30.6, 27.9, 25.6, 24.64, 24.56, 19.4. HRMS calcd. for C₁₂H₂₄BrO₂ (MH⁺): 279.0960, found 279.0955.

Synthesis of compound A. Ethyl 4-bromo-2,2-dimethylbutyrate (11.17g, 50.0 mmol) was dissolved in dry DMF (100 mL) under nitrogen, then were subsequently added 1,3-propanedithiol (2.46 g, 22.7 mmol), tetrabutylammonium iodide (840 mg, 2.2 mmol), and finally 60% NaH in mineral oil (2.0 g, 50 mmol). The mixture was allowed to stir for an hour, then a second portion of 60% NaH in mineral oil (2g, 50 mmol) was added. The reaction mixture was then heated to 80 °C for 3 hours. After cooling, the reaction was quenched by pouring into ice - water (200 g), and the mixture was acidified with concentrated HCl (100 mL). The resulting aqueous layer was extracted with ethyl acetate (3 x 200 mL). The ethyl acetate solution was then extracted with saturated NaHCO₃ (2 x 300 mL). The basic extracts were then combined and acidified with conc. HCl (200 mL) in an open beaker and allowed to stir for an hour. The now-acidic aqueous layer was extracted with chloroform (3 x 200 mL); the resulting organics were combined and dried over Na₂SO₄. Evaporation produced a clear, yellow oil (8.67 g) which was purified by dissolving in 1M NaOH, treating with activated carbon, extracting the basic layer with chloroform, then reacidifying and extracting with chloroform. This final chloroform layer was dried over 4A molecular sieves and evaporated to yield 2.79 g refined product (purity

est. 95%). ^1H NMR, (300 MHz, CDCl_3), δ (ppm): 11.43 (br s, 2H); 2.61 (t, 4H); 2.48 (t, 4H); 1.89-1.77 (m, 6H). ^{13}C NMR, (75 MHz, CDCl_3), δ (ppm): 183.1, 42.2, 40.6, 30.7, 29.4, 27.4, 25.0.

5 **5.2 Synthesis of 6-(5,5-dimethyl-6-hydroxy-hexyl-sulfanyl)-2,2-dimethyl-hexan-1-ol (Compound B)**

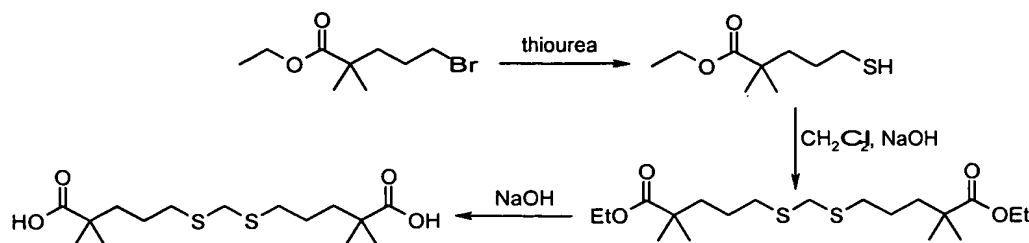


Bis-(5,5-dimethyl-6-tetrahydropyranyloxy-hexyl)-sulfide. A solution of 2-(6-bromo-2,2-dimethyl-hexyloxy)-tetrahydro-pyran ((J-L.H. Dasseux et al. US 6,410,802, 2002; 14.9 g, 50.8 mmol) in ethanol (100 ml) was added dropwise over 30 min to a solution of sodium sulfide nonahydrate (6.10 g, 25.41 mmol) in water (10 ml) at rt under N_2 atmosphere. The reaction mixture was stirred at rt for 18 h and then heated to reflux for 3.5 h. The solution was concentrated *in vacuo*, 5% NaOH (100 ml) was added, and the reaction mixture was extracted with CH_2Cl_2 (200 ml). The organic layer was dried over MgSO_4 , concentrated *in vacuo*, and dried in high *vacuo* to give bis-(5,5-dimethyl-6-tetrahydropyranyloxy-hexyl)-sulfide (9.17 g, 78%) as a slightly yellowish oil. ^1H NMR (300 MHz, CDCl_3), δ (ppm): 4.54 (t, 2 H, $J = 2.9$); 3.83 (m, 2 H); 3.48 (m, 2 H); 3.45 (d, 2 H, $J = 9.2$); 2.98 (d, 2 H, $J = 9.2$); 2.50 (t, 4 H, $J = 7.3$); 1.82 (m, 2 H); 1.75 - 1.44 (m, 16 H); 1.42 - 1.18 (m, 10 H); 0.894 (s, 6 H); 0.887 (s, 6 H). ^{13}C NMR (75 MHz, CDCl_3), δ (ppm): 98.90; 76.26; 61.68; 38.77; 34.04; 32.00; 30.51; 25.44; 24.42; 24.36; 23.20; 19.28. Calcd. for $\text{C}_{26}\text{H}_{51}\text{SO}_4$: 459.3508, found 459.3504.

6-(5,5-dimethyl-6-hydroxy-hexyl-sulfanyl)-2,2-dimethyl-hexan-1-ol. A solution of bis-(5,5-dimethyl-6-tetrahydropyranyloxy-hexyl)-sulfide (9.2 g, 20.0 mmol) in methanol (100 ml) and concd. HCl (10 ml) was heated to reflux for 1.5 h under N_2 atmosphere. The reaction mixture was cooled to rt, concentrated *in vacuo*, diluted with CH_2Cl_2 (250 ml), and extracted with saturated NaHCO_3 solution (2×100 ml) and brine (100 ml). The organic layer was dried over MgSO_4 and concentrated *in vacuo* to give 2 (4.50 g, 15.5 mmol, 77 %) as an oil (stench). In a larger procedure, the crude (152 g) was fractionally distilled under reduced pressure to give a clear light orange oil (90 g, 170-180 $^\circ\text{C}$ / 0.1-0.3 mm Hg, assay 99.2% HPLC). ^1H NMR (300 MHz, CDCl_3), δ (ppm): 3.30 (s, 4 H); 2.52 (t, 4 H, $J = 7.1$);

2.24 (s, 2 H); 1.57 (m, 4 H); 1.42 - 1.18 (m, 8 H); 0.86 (s, 12 H). ^{13}C NMR (75 MHz, CDCl_3), δ (ppm): 71.43, 37.88, 34.86, 31.90, 30.20, 23.78, 22.93. Calcd. for $\text{C}_{16}\text{H}_{35}\text{SO}_2$ (MH $^+$): 291.2358, found 291.2353

5.3 Synthesis of 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid (Compound C)



5-Mercapto-2,2-dimethylpentanoic acid ethyl ester. To a solution of 5-bromo-2,2-dimethylpentanoic acid ethyl ester (2.41 g, 10 mmol) in ethyl alcohol (5 mL) was added thiourea (0.77 g, 10 mmol) and the mixture was refluxed for 3 h under a nitrogen atmosphere. A solution of sodium hydroxide (0.62 g, 15 mmol) in deionized water (2.5 mL) was added and stirring was continued for another 2 h at reflux temperature. The mixture was cooled to rt and the ethanol was distilled off under reduced pressure. Diethyl ether (20 mL) was added and the layers were separated. The organic phase was washed with saturated sodium chloride solution (5 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give 5-mercapto-2,2-dimethylpentanoic acid ethyl ester (1.41 g, 74 %) as a yellow oil. ^1H NMR (300 MHz, CDCl_3/TMS): δ (ppm): 4.12 (q, $J = 7.0$ Hz, 2 H), 2.57 - 2.43 (m, 2 H), 1.69 - 1.45 (m, 4 H), 1.25 (t, $J = 7.0$ Hz, 3 H), 1.17 (s, 7 H). ^{13}C NMR (75 MHz, CDCl_3/TMS): δ (ppm): 177.55, 41.0, 39.24, 25.07, 24.90, 14.18.

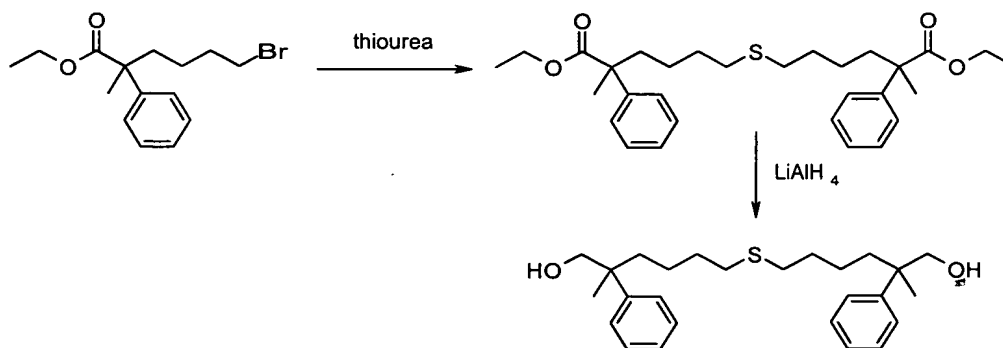
2,2,12,12-Tetramethyl-6,8-dithiatridecane-1,13-dioic acid ethyl ester. A mixture of 5-mercapto-2,2-dimethylpentanoic acid ethyl ester (1.32 g, 7.0 mmol), sodium hydroxide (0.79 g, 19.0 mmol), dichloromethane (11 mL), deionized water (13 mL), and tricaprilmethyl ammonium chloride (26 mg) was stirred vigorously for 20 min at rt. The layers were separated and the organic layer was washed with water (5 mL), dried over magnesium sulfate, and concentrated. The crude product (1.25 g) was purified by column chromatography on silica (hexanes / ethyl acetate = 75 / 25) to afford 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid ethyl ester (0.86 g, 63 %) as a pale oil. ^1H NMR (300

MHz, CDCl₃/TMS): δ (ppm): 4.11 (q, 4 H, $J = 7.1$ Hz), 3.63 (s, 2 H), 2.60 (t, 4 H, $J = 6.8$ Hz), 1.68 - 1.48 (m, 8 H), 1.25 (t, 6 H, $J = 7.1$ Hz), 1.17 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 177.90, 60.54, 42.22, 39.95, 35.41, 31.26, 25.37, 24.72, 14.48. HRMS (LSIMS, nba): Calcd. for C₁₉H₃₆O₄S₂ (M⁺): 392.2055, found 392.2031.

- 5 **2,2,12,12-Tetramethyl-6,8-dithiatridecane-1,13-dioic acid.** A solution of 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid ethyl ester (7.16 g, 18.25 mmol) and sodium hydroxide (3.13 g, 76 mmol) in ethanol (40 mL) and deionized water (4 mL) was heated to reflux for 2 h. The ethanol was evaporated and the residue dissolved in water (30 mL) and extracted with diethyl ether (20 mL). The aqueous layer was acidified with 2 N
- 10 hydrochloric acid to pH 2 and extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with saturated sodium chloride solution (15 mL), dried over MgSO₄, and concentrated to give the crude product (4.79 g) as an oil, which solidified on standing. Recrystallization (hexanes / ethyl acetate = 2 / 1) yielded 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid (2.9 g, 47 %) as nice white needles. Mp.: 72.0 - 72.5 °C).
- 15 ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 11.55 (br, 2 H), 3.65 (s, 2 H), 2.62 (t, $J = 6.8$ Hz, 4 H), 1.70 - 1.51 (m, 8 H), 1.21 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 184.76, 41.99, 39.54, 35.20, 31.07, 24.87, 24.54. HRMS (HR, LSIMS, gly): Calcd. for C₁₅H₂₉O₄S₂ (MH⁺): 337.1507, found 337.1508. Anal. (C₁₅H₂₈O₄S₂) calcd. (found): C, 53.54 (53.38); H, 8.39 (8.26); S, 19.06 (19.29).

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5.4 Synthesis of 6-(6-hydroxy-5-methyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexan-1-ol (Compound D)

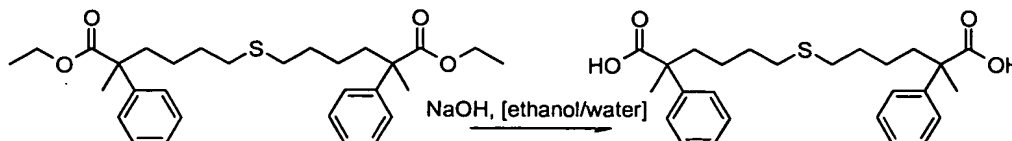


- 25 **6-(5-Ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexanoic acid ethyl ester.** A solution of ethyl 6-bromo-2-methyl-2-phenylhexanoate (18.5 g, 59.0 mmol),

thiourea (7.0 g, 91.0 mmol), and potassium hydroxide (6.1 g, 92.0 mmol) in ethanol (200 mL) was heated to 40 - 50 °C overnight. The mixture was cooled to rt, poured into an ice/water/HCl mixture (150 g/150 mL/150 mL), and stirred for 20 min. The mixture was extracted with dichloromethane (4 - 60 mL) and the combined organic layers were washed with sat. NaHCO₃ solution (100 mL) and sat. NH₄Cl solution (100 mL). The dichloromethane solution was dried over MgSO₄ and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes / ethyl acetate = 10 / 1) to give 6-(5-ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid ethyl ester (12.5 g, 85%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 7.42 - 7.15 (m, 10 H), 4.20 - 4.05 (q, 4 H, *J* = 7.1 Hz), 2.44 (t, *J* = 7.6 Hz, 4 H), 2.15 - 1.95 (m, 2 H), 1.95 - 1.75 (m, 2 H), 1.62 - 1.40 (m, 10 H), 1.35 - 1.10 (m, 4 H), 1.18 (t, 6 H, *J* = 7.1 Hz). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 176.06, 143.89, 128.25, 126.52, 125.84, 60.65, 50.04, 38.77, 31.80, 30.11, 24.06, 22.61, 14.01. HRMS (LSIMS, nba): Calcd. for C₃₀H₄₃O₄S₁ (MH⁺): 499.2882, found 499.2868.

6-(6-Hydroxy-5-methyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexan-1-ol. Under nitrogen atmosphere, to a solution of lithium aluminum hydride (1.0 M solution in diethyl ether, 60 mL, 60 mmol) in diethyl ether (150 mL) was added a solution of 6-(5-ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid ethyl ester (9.45 g, 18 mmol) in anhydrous diethyl ether (50 mL). The reaction mixture was heated to reflux for 3 h and was stirred at rt overnight. The excess of lithium aluminum hydride was carefully quenched by addition of ethyl acetate (20 mL) and the precipitate was completely dissolved with 6 N HCl (10 mL) and water (100 mL). The mixture was extracted with diethyl ether (4 - 60 mL). The combined organic layers were washed with saturated NH₄Cl solution (20 mL), dried over MgSO₄, and concentrated *in vacuo* to give a crude product (6.9 g). Purification by column chromatography on silica gel (hexanes / ethyl acetate = 10 / 1) yielded 6-(6-hydroxy-5-methyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexan-1-ol (5.36 g, 69%) as a yellow oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 7.40 - 7.13 (m, 10 H), 3.69 (d, *J* = 11.0 Hz, 2 H), 3.53 (d, *J* = 11.0 Hz, 2 H), 2.38 (t, *J* = 7.3 Hz, 4 H), 1.85 - 1.63 (m, 2 H), 1.60 (br., 2 H), 1.58 - 1.40 (m, 6 H), 1.40 - 1.20 (m, 2 H), 1.34 (s, 6 H), 1.15 - 0.93 (m, 2 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 144.63, 128.43, 126.62, 126.14, 72.42, 43.34, 37.91, 31.85, 30.31, 23.16, 21.53. HRMS (HR, LSIMS, gly): Calcd. for C₂₆H₃₉O₂S₁ (MH⁺): 415.2671, found: 415.2670. HPLC: 97.3 % purity.

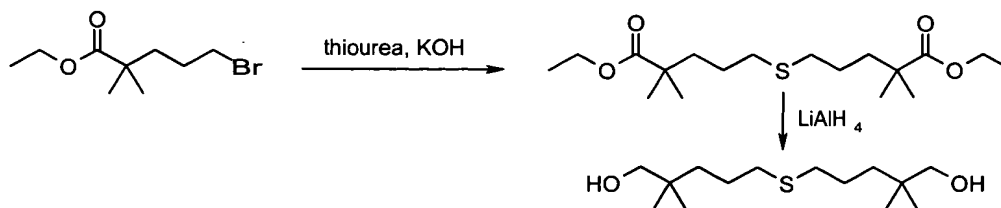
5.5 Synthesis of 6-(5-carboxy-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid (Compound E)



5

6-(5-Carboxy-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid. A solution of 6-(5-ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid ethyl ester (6.00 g, 12.0 mmol) and sodium hydroxide (3.1 g, 74.0 mmol) in ethanol (40 mL) and deionized water (4 mL) was heated to reflux for 2 h. The ethanol was evaporated in vacuo and the residue was dissolved in water (20 mL) and extracted with diethyl ether (20 mL). The organic phase was discarded. The aqueous layer was acidified with 2 N hydrochloric acid (15 ml) to pH 2 - 3 and extracted with diethyl ether (4 - 50 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO_4 , and concentrated *in vacuo*. The residue (4.53 g) was purified by column chromatography on silica gel (hexanes / ethyl acetate = 10 / 1) to give 6-(5-carboxy-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid (3.63 g, 68 %) as a yellowish oil. ^1H NMR (300 MHz, CDCl_3/TMS): δ (ppm): 7.42 - 7.20 (m, 10 H), 2.45 (t, $J = 7.3$ Hz, 4 H), 2.15 - 1.80 (m, 4 H), 1.65 - 1.45 (m, 4 H), 1.56 (s, 6 H), 1.40 - 1.15 (m, 4 H). ^{13}C NMR (75 MHz, CDCl_3/TMS): δ (ppm): 182.43, 142.89, 128.41, 126.91, 126.05, 50.00, 38.53, 31.80, 30.00, 24.03, 22.40. HRMS (LSIMS, nba): Calcd. for $\text{C}_{26}\text{H}_{35}\text{O}_4\text{S}_1$ (MH^+): 443.2256, found: 443.2231.

5.6 Synthesis of di-(6-hydroxy-5,5-dimethylpentyl)sulfide (Compound F)



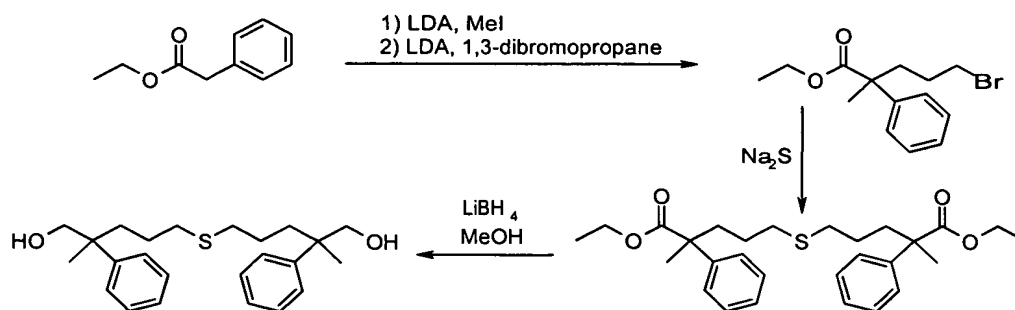
5-(4-Ethoxycarbonyl-4-methyl-pentylsufanyl)-2,2-dimethyl-pentanoic acid ethyl ester.

A solution of ethyl 5-bromo-2,2-dimethylpentanoate (9.1 g, 38.4 mmol), potassium hydroxide (2.69 g, 48.0 mmol), and thiourea (3.65 g, 48.0 mmol) in ethanol (100 mL) was stirred at rt for 10 min and then heated to 40 - 45 °C for one hour. The solution was cooled and ice (100 g), concd. HCl (100 mL), and water (100 mL) were added. The solution was extracted with dichloromethane (3 x 200 mL). The combined organic phases were washed with 5 % NaHCO₃ solution (2 x 200 mL) and sat. NH₄Cl solution (300 mL), then dried over Na₂SO₄ and concentrated in vacuo to yield 5-(4-ethoxycarbonyl-4-methyl-pentylsufanyl)-2,2-dimethyl-pentanoic acid ethyl ester (6.57 g, 90 %) as a clear, pale yellow oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 4.11 (q, 4 H, *J* = 7.1 Hz), 2.47 (t, 4 H, *J* = 6.9 Hz), 1.70 - 1.46 (m, 8 H), 1.25 (t, 6 H, *J* = 7.1 Hz), 1.17 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 177.5, 60.1, 41.9, 39.7, 32.3, 25.00, 24.95, 14.1. HRMS (LSIMS): Calcd. for C₁₈H₃₅O₄S (MH⁺): 347.2256, found 347.2261.

Di-(6-hydroxy-5,5-dimethylpentyl)sulfide. Under N₂ atmosphere, lithium aluminum hydride (1.0 g, 0.026 mol) was introduced to anhydrous diethyl ether (100 mL) stirred for ten min. To this solution was added a solution of 5-(4-ethoxycarbonyl-4-methyl-pentylsufanyl)-2,2-dimethyl-pentanoic acid ethyl ester (3.10 g, 8.90 mmol) in diethyl ether (50 mL). The reaction mixture was heated to reflux for 3 h and then stirred at rt overnight. The excess of lithium aluminum hydride was decomposed by addition of ethyl acetate (20 mL). The sludge was dissolved in HCl (5 N, 5 mL) and water (50 mL). The mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with saturated NH₄Cl solution (20 mL), dried over MgSO₄, concentrated in vacuo, and dried in high vacuo to give di-(6-hydroxy-5,5-dimethylpentyl)sulfide (2.3 g, 98 %) as an oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 3.31 (s, 4 H), 2.72 (br., 2 H), 2.50 (t, 4 H, *J* = 7.3 Hz), 1.62 - 1.50 (m, 4 H), 1.37 - 1.25 (m, 4 H), 0.87 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 71.61, 37.86, 35.16, 33.21, 24.36, 24.02. HRMS (LSIMS, gly): Calcd. for C₁₄H₃₁O₂S (MH⁺): 263.2045, found 263.2044.

5.7 Synthesis of 5-(5-hydroxy-4-methyl-4-phenylpentylsulfanyl)-2-methyl-2-phenylpentan-1-ol (Compound G)

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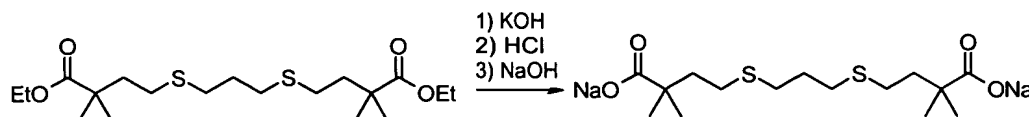
5-Bromo-2-methyl-2-phenyl-pentanoic acid ethyl ester. Under Ar atmosphere, to a solution of ethyl phenylacetate (42.4 g, 0.257 mol) and DMPU (5 mL) in THF (250 mL) was added drop-wise LDA (2.0 M solution in heptane/THF/ethylbenzene, 135 mL, 270 mmol) at -78 °C. After 2 h, methyl iodide (41.40 g, 0.292 mol) was added and the mixture was allowed to warm to rt overnight. This solution was cooled to -78 °C and 1,3-dibromopropane (72.7 g, 0.36 mol) was added. The reaction mixture was allowed to stir overnight, gradually warming to rt. After careful addition of ice (200 g), sat. NH₄Cl solution (400 mL), and concd. HCl (100mL), the mixture was extracted with ethyl acetate (2 x 200 mL). The combined organic layers were dried over MgSO₄, concentrated *in vacuo*, and distilled under reduced pressure to give 5-bromo-2-methyl-2-phenyl-pentanoic acid ethyl ester (88.6 g, 59 %) as a colorless oil (bp.: 122 -128 °C/0.25 mmHg). ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 7.34 - 7.21 (m, 5 H), 4.12 (q, 2 H, *J* = 6.9 Hz), 3.35 (t, 2 H, *J* = 6.6 Hz), 2.20 - 1.95 (m, 2 H), 1.77 - 1.71 (m, 2 H), 1.56 (s, 3 H), 1.18 (t, 3H, *J* = 6.9 Hz). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 175.88, 143.40, 128.54, 126.90, 125.99, 60.96, 49.83, 38.18, 34.01, 28.45, 22.81, 14.17.

5-(4-Ethoxycarbonyl-4-phenyl-pentylsulfanyl)-2-methyl-2-phenyl-pentanoic acid ethyl ester. A solution of sodium sulfide nonahydrate (2.65 g, 0.011 mol) and 5-bromo-2-methyl-2-phenyl-pentanoic acid ethyl ester (6.49 g, 0.022 mol) in water (50 mL) and ethanol (5 mL) was stirred at 40 °C for 20 h and heated to reflux for 1 h. The solution was concentrated in vacuo and 5 % NaOH solution (50 mL) was added. The mixture was extracted with dichloromethane (3 x 50 mL), the combined organic layers were washed with

water (2 x 100 mL), and dried over anhydrous MgSO_4 . The solution was filtered through basic alumina (100 g), which was rinsed with dichloromethane (250 mL). The filtrate was concentrated and dried (100 °C/1 mmHg) to produce 5-(4-ethoxycarbonyl-4-phenyl-pentylsulfanyl)-2-methyl-2-phenyl-pentanoic acid ethyl ester (4.18 g, 85 %) as colorless, viscous oil, which was used without purification in the next step. ^1H NMR (300 MHz, CDCl_3/TMS): δ (ppm): 7.32 - 7.19 (m, 10 H), 4.11 (q, 4 H, $J = 6.9$ Hz), 2.46 - 2.40 (m, 4 H), 2.09 - 1.98 (m, 4 H), 1.54 (s, 6 H), 1.48 (m, 4 H), 1.17 (t, 6 H, $J = 6.9$ Hz). ^{13}C NMR (75 MHz, CDCl_3/TMS): δ (ppm): 176.08, 143.78, 128.47, 126.79, 126.07, 60.92, 50.14, 38.64, 32.54, 24.95, 22.89, 14.25.

5-(5-Hydroxy-4-methyl-4-phenylpentylsulfanyl)-2-methyl-2-phenylpentan-1-ol. Under nitrogen atmosphere, methanol (1.60 g, 50.5 mmol) was added drop-wise to a suspension of LiBH_4 (1.10 g, 50.5 mmol) in dichloromethane (20 mL) at rt. A solution of 5-(4-ethoxycarbonyl-4-phenyl-pentylsulfanyl)-2-methyl-2-phenyl-pentanoic acid ethyl ester (7.75 g, 16.5 mmol) in dichloromethane (100 mL) was added drop-wise at gentle reflux. The mixture was stirred under reflux for 16 h, then cooled to rt and carefully hydrolyzed with 2 N hydrochloric acid (50 mL) and saturated ammonium chloride solution (100 mL). The aqueous layer was extracted with dichloromethane (2×150 mL). The combined organic layers were washed with water (2×100 mL) and dried over anhydrous MgSO_4 . The filtrate was evaporated to yield the crude product (5.55 g) as a colorless, viscous oil. This residue was purified repeatedly by column chromatography on silica gel (120 g, first with dichloromethane / ethyl acetate = 1 : 1, second with dichloromethane / ethyl acetate = 7/1), and dried at 100 °C for 2.5 h under high vacuo to give 5-(5-hydroxy-4-methyl-4-phenylpentylsulfanyl)-2-methyl-2-phenylpentan-1-ol (3.06 g, 41%) as a colorless viscous oil. ^1H NMR (300 MHz, CDCl_3/TMS): δ (ppm): 7.30 (m, 8 H), 7.20 (m, 2 H), 3.65 (m, 2 H), 3.50 (m, 2 H), 2.32 (m, 4 H), 1.82 (dt, $J = 3.9, 9.6$ Hz, 2 H), 1.60 - 1.37 (m, 6 H), 1.32 (s, 6 H), 1.20 - 1.25 (m, 2H). ^{13}C NMR (75 MHz, CDCl_3/TMS): δ (ppm): 144.58, 128.60, 126.81, 126.35, 72.56, 43.42, 37.60, 32.74, 32.71, 23.93, 23.91, 21.6. HRMS (LSIMS, gly): Calcd. for $\text{C}_{24}\text{H}_{35}\text{O}_2\text{S}$ (MH^+): 387.2358, found: 387.2350.

5.8 Synthesis of 2,2,12,12-Tetramethyl-5,9-dithiatridecanedioic acid, disodium salt
(Compound H)

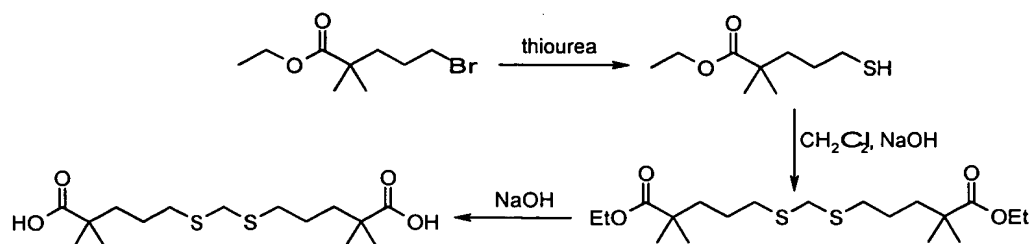


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2,2,12,12-Tetramethyl-5,9-dithiatridecanedioic acid, disodium salt. The starting diester 4-[3-(ethoxycarbonyl-3-methyl-butylsulfanyl)-propylsulfany]-2,2-dimethyl-butyrac acid ethyl ester (6.85 g, 14.0 mmol) and KOH (10.0 g, 178.2 mmol), were dissolved in water (50 mL) and ethanol (200 mL) and heated to reflux for four 4 h. The solvent was evaporated to about 75 mL volume and the mixture diluted with deionized water (75 mL). The solution was extracted with diethyl ether (3 x 100 mL) and the ethereal phases were discarded. The aqueous layer was acidified with concd. HCl (30 mL) and extracted with diethyl ether (3 100 mL). The combined organic layers were washed with sat NH₄Cl solution and concentrated to give the free acid as a colorless oil (4.88 g, 93 %). The disodium salt of 2,2,12,12-tetramethyl-5,9-dithiatridecanedioic acid (4.41 g) was prepared by reacting the free acid with two equivalents of NaOH (1.16 g, 29.0 mmol) and evaporating to dryness. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): (free acid) 12.2 (br s, 2H), 2.56 (t, 4 H, *J* = 7.1 Hz), 2.39 (t, 4 H, *J* = 8.4 Hz), 1.80 - 1.65 (m, 6 H), 1.10 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 178.3, 46.4, 29.8, 28.9, 26.7, 25.6, 24.7.

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5.9 Synthesis of 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid
(Compound I)



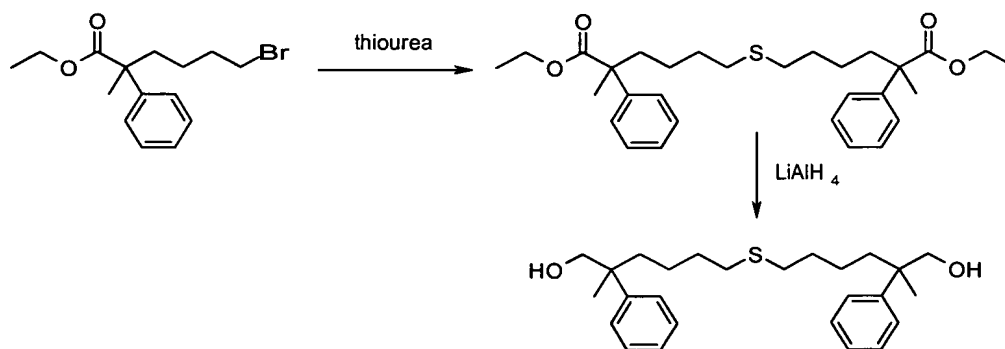
5-Mercapto-2,2-dimethylpentanoic acid ethyl ester. To a solution of 5-bromo-2,2-

5 dimethylpentanoic acid ethyl ester (2.41 g, 10 mmol) in ethyl alcohol (5 mL) was added thiourea (0.77 g, 10 mmol) and the mixture was refluxed for 3 h under a nitrogen atmosphere. A solution of sodium hydroxide (0.62 g, 15 mmol) in deionized water (2.5 mL) was added and stirring was continued for another 2 h at reflux temperature. The mixture was cooled to rt and the ethanol was distilled off under reduced pressure. Diethyl
 10 ether (20 mL) was added and the layers were separated. The organic phase was washed with saturated sodium chloride solution (5 mL), dried over sodium sulfate, filtered, and concentrated in vacuo to give 5-mercapto-2,2-dimethylpentanoic acid ethyl ester (1.41 g, 74 %)
 15 as a yellow oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 4.12 (q, *J* = 7.0 Hz, 2 H), 2.57 - 2.43 (m, 2 H), 1.69 - 1.45 (m, 4 H), 1.25 (t, *J* = 7.0 Hz, 3 H), 1.17 (s, 7 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 177.55, 41.0, 39.24, 25.07, 24.90, 14.18.

2,2,12,12-Tetramethyl-6,8-dithiatridecane-1,13-dioic acid ethyl ester. A mixture of 5-mercapto-2,2-dimethylpentanoic acid ethyl ester (1.32 g, 7.0 mmol), sodium hydroxide (0.79 g, 19.0 mmol), dichloromethane (11 mL), deionized water (13 mL), and tricaprylmethyl ammonium chloride (26 mg) was stirred vigorously for 20 min at rt. The
 20 layers were separated and the organic layer was washed with water (5 mL), dried over magnesium sulfate, and concentrated. The crude product (1.25 g) was purified by column chromatography on silica (hexanes / ethyl acetate = 75 / 25) to afford 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid ethyl ester (0.86 g, 63 %) as a pale oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 4.11 (q, 4 H, *J* = 7.1 Hz), 3.63 (s, 2 H), 2.60 (t, 4 H, *J* = 6.8 Hz), 1.68 - 1.48 (m, 8 H), 1.25 (t, 6 H, *J* = 7.1 Hz), 1.17 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 177.90, 60.54, 42.22, 39.95, 35.41, 31.26, 25.37, 24.72, 14.48.
 25 HRMS (LSIMS, nba): Calcd. for C₁₉H₃₆O₄S₂ (M⁺): 392.2055, found 392.2031.

2,2,12,12-Tetramethyl-6,8-dithiatridecane-1,13-dioic acid. A solution of 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid ethyl ester (7.16 g, 18.25 mmol) and sodium hydroxide (3.13 g, 76 mmol) in ethanol (40 mL) and deionized water (4 mL) was heated to reflux for 2 h. The ethanol was evaporated and the residue dissolved in water (30 mL) and extracted with diethyl ether (20 mL). The aqueous layer was acidified with 2 N hydrochloric acid to pH 2 and extracted with diethyl ether (2 x 20 mL). The combined organic layers were washed with saturated sodium chloride solution (15 mL), dried over MgSO₄, and concentrated to give the crude product (4.79 g) as an oil, which solidified on standing. Recrystallization (hexanes / ethyl acetate = 2 / 1) yielded 2,2,12,12-tetramethyl-6,8-dithiatridecane-1,13-dioic acid (2.9 g, 47 %) as nice white needles. Mp.: 72.0 - 72.5 °C). ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 11.55 (br, 2 H), 3.65 (s, 2 H), 2.62 (t, *J* = 6.8 Hz, 4 H), 1.70 - 1.51 (m, 8 H), 1.21 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 184.76, 41.99, 39.54, 35.20, 31.07, 24.87, 24.54. HRMS (HR, LSIMS, gly): Calcd. for C₁₅H₂₉O₄S₂ (MH⁺): 337.1507, found 337.1508. Anal. (C₁₅H₂₈O₄S₂) calcd. (found): C, 53.54 (53.38); H, 8.39 (8.26); S, 19.06 (19.29).

5.10 Synthesis of 6-(6-Hydroxy-5-methyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexan-1-ol (Compound J)

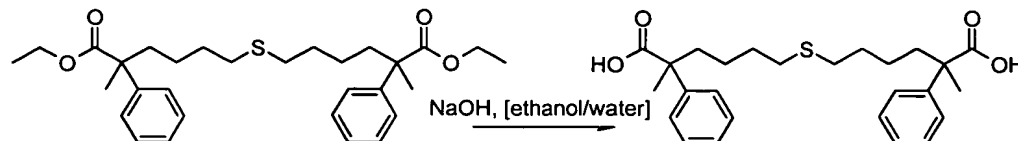


6-(5-Ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexanoic acid ethyl ester. A solution of ethyl 6-bromo-2-methyl-2-phenylhexanoate (18.5 g, 59.0 mmol), thiourea (7.0 g, 91.0 mmol), and potassium hydroxide (6.1 g, 92.0 mmol) in ethanol (200 mL) was heated to 40 - 50 °C overnight. The mixture was cooled to rt, poured into an ice/water/HCl mixture (150 g/150 mL/150 mL), and stirred for 20 min. The mixture was extracted with dichloromethane (4 x 60 mL) and the combined organic layers were washed with sat. NaHCO₃ solution (100 mL) and sat. NH₄Cl solution (100 mL). The

dichloromethane solution was dried over MgSO_4 and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexanes / ethyl acetate = 10 / 1) to give 6-(5-ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid ethyl ester (12.5 g, 85%) as a yellow oil. ^1H NMR (300 MHz, CDCl_3/TMS): δ (ppm): 7.42 - 7.15 (m, 10 H), 4.20 - 4.05 (q, 4 H, $J = 7.1$ Hz), 2.44 (t, $J = 7.6$ Hz, 4 H), 2.15 - 1.95 (m, 2 H), 1.95 - 1.75 (m, 2 H), 1.62 - 1.40 (m, 10 H), 1.35 - 1.10 (m, 4 H), 1.18 (t, 6 H, $J = 7.1$ Hz). ^{13}C NMR (75 MHz, CDCl_3/TMS): δ (ppm): 176.06, 143.89, 128.25, 126.52, 125.84, 60.65, 50.04, 38.77, 31.80, 30.11, 24.06, 22.61, 14.01. HRMS (LSIMS, nba): Calcd. for $\text{C}_{30}\text{H}_{43}\text{O}_4\text{S}_1$ (MH^+): 499.2882, found 499.2868.

6-(6-Hydroxy-5-methyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexan-1-ol. Under nitrogen atmosphere, to a solution of lithium aluminum hydride (1.0 M solution in diethyl ether, 60 mL, 60 mmol) in diethyl ether (150 mL) was added a solution of 6-(5-ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid ethyl ester (9.45 g, 18 mmol) in anhydrous diethyl ether (50 mL). The reaction mixture was heated to reflux for 3 h and was stirred at rt overnight. The excess of lithium aluminum hydride was carefully quenched by addition of ethyl acetate (20 mL) and the precipitate was completely dissolved with 6 N HCl (10 mL) and water (100 mL). The mixture was extracted with diethyl ether (4 - 60 mL). The combined organic layers were washed with saturated NH_4Cl solution (20 mL), dried over MgSO_4 , and concentrated *in vacuo* to give a crude product (6.9 g). Purification by column chromatography on silica gel (hexanes / ethyl acetate = 10 / 1) yielded 6-(6-hydroxy-5-methyl-5-phenylhexylsulfanyl)-2-methyl-2-phenylhexan-1-ol (5.36 g, 69%) as a yellow oil. ^1H NMR (300 MHz, CDCl_3/TMS): δ (ppm): 7.40 - 7.13 (m, 10 H), 3.69 (d, $J = 11.0$ Hz, 2 H), 3.53 (d, $J = 11.0$ Hz, 2 H), 2.38 (t, $J = 7.3$ Hz, 4 H), 1.85 - 1.63 (m, 2 H), 1.60 (br., 2 H), 1.58 - 1.40 (m, 6 H), 1.40 - 1.20 (m, 2 H), 1.34 (s, 6 H), 1.15 - 0.93 (m, 2 H). ^{13}C NMR (75 MHz, CDCl_3/TMS): δ (ppm): 144.63, 128.43, 126.62, 126.14, 72.42, 43.34, 37.91, 31.85, 30.31, 23.16, 21.53. HRMS (HR, LSIMS, gly): Calcd. for $\text{C}_{26}\text{H}_{39}\text{O}_2\text{S}_1$ (MH^+): 415.2671, found: 415.2670. HPLC: 97.3 % purity.

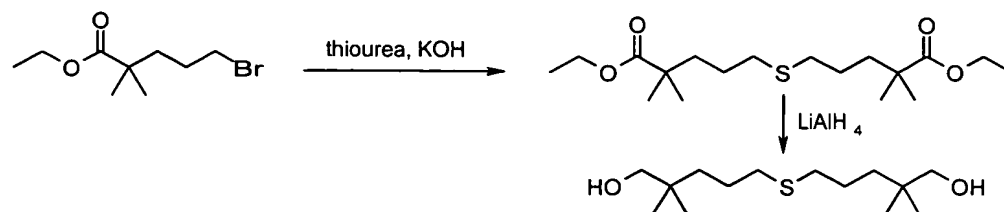
5.11 Synthesis of 6-(5-Carboxy-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid (Compound K)



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6-(5-Carboxy-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid. A solution of 6-(5-ethoxycarbonyl-5-phenylhexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid ethyl ester (6.00 g, 12.0 mmol) and sodium hydroxide (3.1 g, 74.0 mmol) in ethanol (40 mL) and deionized water (4 mL) was heated to reflux for 2 h. The ethanol was evaporated in vacuo and the residue was dissolved in water (20 mL) and extracted with diethyl ether (20 mL). The organic phase was discarded. The aqueous layer was acidified with 2 N hydrochloric acid (15 mL) to pH 2 - 3 and extracted with diethyl ether (4 - 50 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO₄, and concentrated *in vacuo*. The residue (4.53 g) was purified by column chromatography on silica gel (hexanes / ethyl acetate = 10 / 1) to give 6-(5-carboxy-5-phenyl-hexylsulfanyl)-2-methyl-2-phenyl-hexanoic acid (3.63 g, 68 %) as a yellowish oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 7.42 - 7.20 (m, 10 H), 2.45 (t, *J* = 7.3 Hz, 4 H), 2.15 - 1.80 (m, 4 H), 1.65 - 1.45 (m, 4 H), 1.56 (s, 6 H), 1.40 - 1.15 (m, 4 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 182.43, 142.89, 128.41, 126.91, 126.05, 50.00, 38.53, 31.80, 30.00, 24.03, 22.40. HRMS (LSIMS, nba): Calcd. for C₂₆H₃₅O₄S₁ (MH⁺): 443.2256, found: 443.2231. The ester (6.0 g, 12 mmol) was dissolved in absolute ethanol (40 mL). Solution of sodium hydroxide (3.1 g, 97%, 74 mmol) in DI water (4 mL) was added to the ester solution. The reaction mixture was stirred and heated to reflux for 2 h, then cooled to rt. Evaporation of EtOH in vacuo gave a yellow oily residue, which was dissolved in water (20 mL) and washed with ethyl ether (20 mL). The organic phase was separated and discarded. The aqueous layer was acidified with 2N hydrochloric acid to pH = 2-3 (15 mL). The product was extracted with diethyl ether (4x50 mL). Combined organic layers were washed with brine (15 mL), dried over MgSO₄. Evaporation of solvent gave the crude product as a yellow oil (4.53 g, 85%), which was purified by column chromatography on silica gel using a mixture of hexanes/EtOAc (10:1) as an eluent. The pure compound was obtained as a yellow oil (3.63 g, 68%).

5.12 Synthesis of di-(6-hydroxy-5,5-dimethylpentyl)sulfide (Compound L)



5 **5-(4-Ethoxycarbonyl-4-methyl-pentylsufanyl)-2,2-dimethyl-pentanoic acid ethyl ester.**

A solution of ethyl 5-bromo-2,2-dimethylpentanoate (9.1 g, 38.4 mmol), potassium hydroxide (2.69 g, 48.0 mmol), and thiourea (3.65 g, 48.0 mmol) in ethanol (100 mL) was stirred at rt for 10 min and then heated to 40 - 45 °C for one hour. The solution was cooled and ice (100 g), concd. HCl (100 mL), and water (100 mL) were added. The solution was extracted with dichloromethane (3 x 200 mL). The combined organic phases were washed with 5 % NaHCO₃ solution (2 x 200 mL) and sat. NH₄Cl solution (300 mL), then dried over Na₂SO₄ and concentrated in vacuo to yield 5-(4-ethoxycarbonyl-4-methyl-pentylsufanyl)-2,2-dimethyl-pentanoic acid ethyl ester (6.57 g, 90 %) as a clear, pale yellow oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 4.11 (q, 4 H, *J* = 7.1 Hz), 2.47 (t, 4 H, *J* = 6.9 Hz), 1.70 - 1.46 (m, 8 H), 1.25 (t, 6 H, *J* = 7.1 Hz), 1.17 (s, 12 H). ¹³C NMR (75 MHz, CDCl₃/TMS): δ (ppm): 177.5, 60.1, 41.9, 39.7, 32.3, 25.00, 24.95, 14.1. HRMS (LSIMS): Calcd. for C₁₈H₃₅O₄S (MH⁺): 347.2256, found 347.2261.

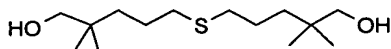
Di-(6-hydroxy-5,5-dimethylpentyl)sulfide. Under N₂ atmosphere, lithium aluminum hydride (1.0 g, 0.026 mol) was introduced to anhydrous diethyl ether (100 mL) stirred for ten min. To this solution was added a solution of 5-(4-ethoxycarbonyl-4-methyl-pentylsufanyl)-2,2-dimethyl-pentanoic acid ethyl ester (3.10 g, 8.90 mmol) in diethyl ether (50 mL). The reaction mixture was heated to reflux for 3 h and then stirred at rt overnight. The excess of lithium aluminum hydride was decomposed by addition of ethyl acetate (20 mL). The sludge was dissolved in HCl (5 N, 5 mL) and water (50 mL). The mixture was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with saturated NH₄Cl solution (20 mL), dried over MgSO₄, concentrated in vacuo, and dried in high vacuo to give di-(6-hydroxy-5,5-dimethylpentyl)sulfide (2.3 g, 98 %) as an oil. ¹H NMR (300 MHz, CDCl₃/TMS): δ (ppm): 3.31 (s, 4 H), 2.72 (br., 2 H), 2.50 (t, 4 H, *J* = 7.3 Hz), 1.62 - 1.50 (m, 4 H), 1.37 - 1.25 (m, 4 H), 0.87 (s, 12 H). ¹³C NMR (75 MHz,

CDCl₃/TMS): δ (ppm): 71.61, 37.86, 35.16, 33.21, 24.36, 24.02. HRMS (LSIMS, gly):
Calcd. for C₁₄H₃₁O₂S (MH⁺): 263.2045, found 263.2044.

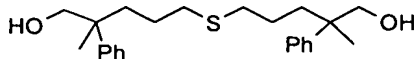
6. BIOLOGICAL ASSAYS

5 6.1 Effects of Illustrative Compounds of the Invention on NonHDL Cholesterol, HDL Cholesterol, Triglyceride Levels, Glycemic Control indicators and Body Weight Control in Obese Female Zucker Rats

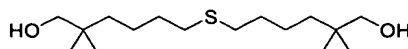
In a number of different experiments, illustrative compounds of the invention are administered daily at a dose of up to 100 mg/kg to chow fed obese female Zucker rats for fourteen days in the morning by oral gavage in 1.5% carboxymethylcellulose/0.2% Tween 20 or 20% ethanol/80% polyethylene glycol (dosing vehicles). Animals are weighed daily. Animals are allowed free access to rodent chow and water throughout the study except on days of blood sampling where food is restricted for six hours prior to blood sampling. Blood glucose is determined after the 6 hour fast in the afternoon without
15 anesthesia from a tail vein. Serum is also prepared from pretreatment blood samples subsequently obtained from the orbital venous plexus (with O₂/CO₂ anesthesia) and following the fourteenth dose at sacrifice from the heart following O₂/CO₂ anesthesia. Serums are assayed for lipoprotein cholesterol profiles, triglycerides, total cholesterol, NonHDL cholesterol, HDL cholesterol, the ratio of HDL cholesterol to that of Non HDL
20 cholesterol, insulin, non esterified fatty acids, and beta hydroxy butyric acid. The percent body weight gain and the ratio of liver to body weight is also determined. These are shown as absolute values or as a percent change of the pretreatment values in Table A.



25 **Compound AA**



Compound BB



Compound CC

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Table A: Examples of effects of oral daily treatment of obese female Zucker rats with compounds of the invention for fourteen days. Values are the percent change from study prebleed.

Compound		Dose (mg/kg/day)	TG	TC	Non- HDL-C	HDL-C	Glucose	Insulin
Compound AA	1	30	-51	21	-40	54	12	-30
	2	30	-34	21	-14	40	7	-36
Compound BB	1	100	-18	-8	-26	9	0	-34
	2	100	1	4	8	2	10	-6
Compound CC	1	30	-29	33	-22	85	2	23
	2	30	-33	97	6	168	15	-20

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The present invention is not to be limited in scope by the specific embodiments disclosed in the examples which are intended as illustrations of a few aspects of the invention and any embodiments which are functionally equivalent are within the scope of this invention. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art and are intended to fall within the appended claims.

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